Draft Comparative Effectiveness Review

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Management of Insomnia Disorder

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Management of Chronic Insomnia

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and safety of treatments for insomnia disorder in the general adult population and in older adults.

Data sources. Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and PSYCINFO bibliographic databases; hand searches of references of relevant studies.

Review methods. Two investigators screened abstracts and full-text articles of identified references for eligibility. Eligible studies included systematic reviews and randomized controlled trials enrolling participants with clinically diagnosed insomnia disorder. We analyzed data for global outcomes (measures that assess both sleep and daytime functioning associated with sleep), sleep outcomes, and adverse effects. We extracted data, assessed risk of bias for randomized controlled trials, assessed quality of relevant systematic reviews, and evaluated strength of evidence for each comparison and outcome. Pooled estimates were analyzed to assess the efficacy and comparative effectiveness of a wide variety of treatments.

Results. We identified 102 eligible publications (95 unique RCTs and 6 unique systematic reviews) as of November 2013 evaluating psychological, pharmacologic, complementary, and alternative medicine interventions reporting on 169 randomized controlled trials. Minimally important differences in outcomes were often not well established or used. Cognitive behavioral therapy for insomnia (CBT-I) improves global outcomes by minimum important differences and modestly improves most sleep outcomes in the general adult population (low to moderate strength of evidence). Evidence on the efficacy of relaxation and stimulus control demonstrated improvements in some sleep outcomes (low strength evidence) in this population. Among older adults, CBT-I and brief behavioral therapy (BBT-I) improved wake time after sleep onset and sleep efficiency (low to moderate strength evidence). BBT-I also improved global outcomes (low strength evidence) and sleep onset latency (moderate strength evidence). Adverse effects were infrequently reported (insufficient evidence). Nonbenzodiazepine hypnotics are efficacious in the general adult population with respect to global and sleep outcomes. Eszopiclone and zolpidem 'as needed' improved global outcomes (low strength evidence); all nonbenzodiazepine hypnotics improved some sleep outcomes (low to moderate strength evidence), but mean effect sizes were larger with eszopiclone, zolpidem, and zolpidem 'as needed.' Evidence on adverse effects from nonbenzodiazepine hypnotics compared with placebo were mixed with few significant differences (insufficient to moderate strength evidence). Melatonin PR decreased sleep onset latency; evidence was insufficient for other sleep outcomes and adverse effects. Ramelteon was similar to placebo for two sleep outcomes (low strength evidence) in the general adult population; evidence for adverse effects was mixed – similar study withdrawals and number reporting more than one adverse effect but higher overall withdrawals(low strength evidence). Evidence on benzodiazepines was insufficient for all outcomes and populations. Evidence for antidepressants was also limited and insufficient for most outcomes. Doxepin improved global outcomes in older adults (low strength evidence) without significant adverse effects (low to moderate strength evidence). This improvement was not clinically significant.

Conclusions. A large number of trials have been conducted to determine effective treatments for insomnia disorder. CBT-I and BBT are safe and effective. Nonbenzodiazepines are effective

without serious adverse effects in the short term. Broad applicability, comparative effectiveness and long-term efficacy and harms of drug treatments are less well understood.

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Executive Summary

Introduction

Sleep problems are some of the most common concerns for adults.[1] Compromised sleep is associated with a decline in overall and sleep related health status and perception of poor health, which can lead to negative personal and social consequences.[2] Individuals with sleep problems also report higher levels of anxiety, depressed mood, physical pain and discomfort, and cognitive deficiencies.[3] Insomnia may be associated with long-term health consequences, including increased morbidity, respiratory disease, rheumatic disease, cardiovascular disease, cerebrovascular conditions, and diabetes.[2]

The term insomnia is variously defined to describe a symptom and/or a disorder. It involves dissatisfaction with sleep quantity or quality and is associated with one or more of the following subjective complaint(s): difficulty with sleep initiation, difficulty maintaining sleep, or early morning waking with inability to return to sleep.[4] Insomnia disorder should be diagnosed in accordance with criteria from the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) and/or the International Classification of Sleep Disorders (ICSD). Both criteria (in current and previous versions) define sleep-related complaint(s) despite adequate opportunity for sleep combined with distress or dysfunction created by the sleep difficulty. The DSM-5 defines insomnia disorder when sleep problems and associated distress/dysfunction last longer than 3 months.[4]

Between 6 and 10 percent of adults have insomnia that meets established diagnostic criteria.[1,4-6] Previous diagnostic criteria for insomnia did not specify a minimum timeframe for sleep difficulties; chronic insomnia (now called insomnia disorder) was used to describe cases that lasted from weeks to months, and insomnia was considered chronic in 40 – 70 percent of insomnia cases.[6]

Several factors are associated with insomnia. Women are 1.4 times more likely than men to suffer from insomnia.[7] Older adults also have higher prevalence of insomnia; aging is often accompanied by changes in sleep patterns (disrupted sleep, frequent waking, early waking) that can lead to insomnia.[8] Older adults typically report difficulty maintaining sleep.[9] Additionally, about half of insomnia cases coexist with a psychiatric diagnosis.[10] Other medical conditions also coexist with or lead to poor sleep, including pulmonary, cardiovascular and arthritic diseases.

Once insomnia disorder is accurately diagnosed, many treatments are available, including over-the-counter medications and supplements, education on sleep hygiene and recommended lifestyle changes, behavioral and psychological interventions, prescription medications, and complementary and alternative (CAM) treatments.

The American Academy of Sleep Medicine (AASM) practice parameters state that psychological and behavioral interventions are effective and recommended for adults.[11] These recommendations were supported by the highest quality evidence.[12] Support for short-term use of pharmacological interventions was based on consensus.[12] An updated AASM evidence synthesis and recommendations on pharmacologic interventions is underway.[13]

Examples of psychological interventions (Table A) include cognitive behavioral therapy (CBT-I), brief behavioral therapy (BBT), and other behavioral interventions alone (i.e., stimulus control, relaxation strategies, sleep restriction).

Prescription drugs are often used to treat insomnia. Several drugs are approved by the Food and Drug Administration (FDA)(doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon). Several other prescription medications

from various drug classes (e.g., antidepressants, antipsychotics) are used off-label. Melatonin is a commonly used over-the-counter insomnia treatment.

Efficacy research has also been conducted on a variety of CAM approaches (Chinese herbal medicine, acupuncture, reflexology, Suanzaoren decoction, etc.). Unfortunately, methodological limitations have prevented conclusive evidence synthesis for these treatments.[14-23]

Insomnia treatment goals include meaningful improvements in sleep and associated distress and/or dysfunction. Insomnia treatment may affect several outcomes. We categorize outcomes as global, sleep, or secondary. Global outcomes measure improvements in sleep and the accompanying daytime dysfunction or distress simultaneously. Two instruments that measure global outcomes include the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). Sleep outcomes measure specific sleep parameters and sleep quality. Specific sleep parameters include sleep-onset latency, wake after sleep onset, total sleep time, and a more comprehensive sleep measure, sleep efficiency (total sleep time/total time in bed). Improvements in specific sleep measures can be assessed objectively or subjectively. Sleep parameters can be objectively measured with polysomnography (measuring sleep continuity parameters, sleep time spent in each stage in a sleep lab) or actigraphy (measuring body movements). Subjective measures are generally believed more clinically valuable because they are patient-centered. Sleep quality, subjectively measured in a variety of ways, is also an important sleep outcome. Secondary outcomes such as daytime fatigue or sleepiness, mood, or quality of life reflect improvements associated with improved sleep.

Several systematic reviews have assessed the efficacy and comparative effectiveness of insomnia treatment. Available reviews, however, do not incorporate the broad range of interventions (psychological, pharmacologic, CAM). This review uses previous systematic reviews and randomized-controlled trials (RCTs) to provide a comprehensive up-to-date synthesis of the evidence on efficacy and comparative effectiveness of insomnia disorder treatments.

Table A. Psychological/behavioral interventions for insomnia disorder

Psychological and Behavioral Treatments for Insomnia	Definition
Sleep hygiene education	Behavioral intervention aiming to educate patients about health and environmental factors they can change to improve sleep.
Stimulus control	Behavioral treatment that aims to change behaviors associated with bed and bedroom and establish consistency in sleep patterns.
Sleep restriction	Behavioral intervention that limits time in bed to sleep time, gradually increasing as sleep efficiency improves.
Relaxation training	Training to reduce somatic tension and control bedtime thought patterns that impair sleep.
Cognitive behavior therapy	Combination treatments that include cognitive and behavioral components.
Multicomponent therapy (i.e., Brief Behavioral Treatment)	Multicomponent behavioral therapies without cognitive therapy
Paradoxical intention	Instructing the patients to remain awake and avoid asleep, eliminating performance anxiety.
Biofeedback	Providing visual or auditory feedback to assist them in controlling tension and arousal.
Imagery training	Visualization techniques focusing on pleasant or neutral images to block out thoughts that impair sleep.
Cognitive behavior therapy	Combination treatments that include cognitive and behavioral components.

Adapted from Morgenthaler T, Kramer M, Alessi C, et al.[11]

Scope and Key Questions

Our review addresses the following key questions and PICOTs:

Key Question 1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

a. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in specific subgroups of adults?
b. What are the efficacy and comparative effectiveness of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for the treatment of insomnia disorder in adults?
c. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

Key Question 2. What are the harms of treatments for insomnia disorder in adults?

b. What are the harms of treatments for insomnia disorder in specific subgroups of adults?
c. What are the harms of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for insomnia disorder in adults?
d. What are the long-term harms of treatments for insomnia disorder in adults?

PICOTS

Population(s)

- Adults, age 18 and above, with insomnia disorder (i.e., insomnia definitions that match insomnia disorder diagnostic criteria)
    - older adults (over age 55)

Intervention Categories

- Psychological
- Pharmaceutical (available in the United States)
- CAM

Comparators

- Drug and CAM efficacy trials must be double-blind placebo controlled.
- Psychological therapy efficacy trials can be controlled with usual care (i.e., sleep hygiene or sleep education) or wait-list controls, or other insomnia treatment.
- Comparative effectiveness trials must include at least two arms of active therapy approved and available in the United States.

Outcomes

- KQ1
    - Global outcomes
        - Measures that incorporate both patients' reported improvement in sleep and daytime functioning or distress.
          Measurement: Questionnaires that include items related to sleep problems and daytime functioning or distress. [ISI;[12,24] Clinical Global Impression Scale (CGIS);[24] PSQI;[11,24] Patient Global Impression Scale (PGIs)].

- Sleep outcomes
  - Patient-reported sleep parameters derived from sleep diaries or questionnaires (sleep-onset latency, number of awakenings, wake after sleep onset, total sleep time, sleep efficiency [total sleep time/total time in bed], and sleep quality.
- Secondary outcomes
  - Mood/wellbeing and quality of life
    Measurement: Assessments derived from questionnaires: Beck Depression Inventory (BDI);[12,24] State-Trait Anxiety Inventory (STAI);[12,24] Profile of Mood States;[24] Quality of Life/Functional Status, Short-form Health Survey (SF-36);[12,24] Sickness Impact Profile Scale;[24] World Health Organization Quality of Life (WHOQOL)[24]; Epworth Sleepiness scale (ESS);[12] Fatigue Severity Scale (FSS).[12,24]

- KQ2
  - Adverse effects of intervention(s)
    - Withdrawals, withdrawals due to interventions, and more than one adverse effect.

Timing

- KQ1: Treatment duration of at least 4 weeks; Outcomes measured at 4 weeks to 3 months after initiation of treatment will be used to assess efficacy/comparative effectiveness and adverse effects.
- KQ1c. Followup measures beyond 3 months of treatment will be used to evaluate longer-term efficacy/comparative effectiveness and adverse effects.

Settings

- Any outpatient setting.

Methods

We searched Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Library to identify previous systematic reviews and RCTs published and indexed in bibliographic databases from 2004 through November 2013. Our search strategy included relevant medical subject headings and natural language terms for the concept of insomnia. This concept was combined with filters to select RCTs and systematic reviews. We relied on several previous systematic reviews to identify relevant studies published prior to 2004. These systematic reviews provided comprehensive coverage of the literature prior to 2004. Bibliographic database searches were supplemented with backward citation searches of highly relevant (address similar KQs and PICOTS) systematic reviews. We will update searches while the draft report is under public/peer review.

Two independent investigators reviewed titles and abstracts of search results. Citations deemed eligible by either investigator underwent full-text screening. Two investigators independently screened full text to determine if inclusion criteria were met. Discrepancies in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We documented the inclusion and exclusion status of citations undergoing full-text screening.

We used data from relevant comparisons in previous systematic reviews to replace the *de novo* extraction process when the comparison was relevant, the methodology was fair or high quality according to an AMSTAR (A Measurement Tool to Assess Systematic Reviews) assessment, and a reliable strength of evidence assessment was conducted (or the information necessary to assess strength of evidence). Data from RCTs in included systematic reviews was not extracted separately to avoid double counting study results. Results of previous systematic

reviews used in lieu of de novo extraction were updated with new data when additional relevant studies were identified.

Remaining RCTs meeting inclusion criteria were assessed for risk of bias and data extraction. One investigator extracted relevant study, population demographic, and outcomes data. Outcomes data used in analyses were confirmed by a second investigator. Outcomes data that was not used in meta-analysis will be confirmed in final tables prior to submitting to Systematic Review Data Repository. Data fields extracted included author, year of publication, setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, duration), followup duration, participant baseline demographics, comorbidities, insomnia definition, method of diagnosis and severity, descriptions and results of primary outcomes and adverse effects, and study funding source. Relevant data were extracted into Excel spreadsheets for descriptive analysis. Total withdrawals, withdrawals due to intervention, and proportion with more than one adverse effect were extracted and analyzed for adverse effects. Data were analyzed in RevMan 5.2[25] software.

We used AMSTAR criteria[26] to assess risk of bias for eligible systematic reviews. Systematic review quality assessment included items such as *a priori* design, dual review, and individual study risk of bias assessment. Two investigators independently assessed risk of bias for RCTs using questionnaires developed from the Cochrane Risk of Bias tool for included studies. The seven domains included in this tool were sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (i.e., was incomplete outcome data adequately addressed), selective reporting, and other sources of bias (i.e., problems not covered by other domains). Additional items were added to assess potential sources of risk of bias were adapted from the RTI item bank for assessing risk of bias in observational studies.[27] These items (such as adequacy of intervention definition and implementation) were especially necessary to adequately capture all potential risk of bias associated with psychological interventions. Each investigator summarized overall risk of bias for each study and classified it as low, moderate, or high based upon their subjective summary risk of bias across domains and confidence that the results are believable given the study's limitations. Overall risk of bias assessments reflected investigators' subjective assessment of confidence that results were believable given the studies limitations. Studies that were included in previous systematic reviews were assessed for risk of bias if we used data for a comparison not addressed in the previous systematic review. Results from different investigators were aggregated to arrive at an overall risk of bias assessments. Studies that were assessed as high risk of bias by two investigators were excluded from analysis. Studies identified in previous systematic reviews were assessed for risk of bias using our methodology. Studies that previous systematic reviews assessed as high risk of bias were excluded from our review.

We synthesized evidence for each unique population, comparison, and outcome combination. When a comparison was adequately addressed by a previous systematic review of acceptable quality (AMSTAR) and no new studies were available, we reiterated the conclusions drawn from that review strength of evidence was assessed using AHRQ methodology with data provided. When new trials were available, previous systematic review data was synthesized with data from additional trials.

We summarized included study characteristics and outcomes in evidence tables. We assessed the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[28] Pooling was conducted when populations, interventions, and outcomes were sufficiently similar. Meta-analysis was performed using random effects models

(DerSimonian and Laird models using RevMan 5.2[25] software). We calculated risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary primary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs were calculated for continuous outcomes. We assessed statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.[28] When pooling was not appropriate due to lack of comparable studies or heterogeneity, we conducted qualitative synthesis using a vote-counting method.

We attempted to identify minimum important differences to assess efficacy and comparative effectiveness of global outcomes and sleep outcomes (Table B). When minimum important differences were clearly established, these were used to determine efficacy or comparative effectiveness. We identified minimum important differences for several outcome measures. These minimum important differences were not widely used in the literature and were typically defined to describe a clinical improvement over baseline, so use of these minimum important differences to assess changes from placebo may not be ideal. Therefore, we reported outcomes defined as minimum important differences, statistically significant differences that exceed minimum important differences, and statistical differences. When we did not find an established minimum important difference in the literature, we used statistical differences to assess efficacy and comparative effectiveness.

Table B. Minimum important differences for determining efficacy and comparative effectiveness

Outcome	Measurement/Instrument Properties	MIDs Reported in Literature
Global Outcomes -		
Insomnia Severity Index	7 Likert items; range 0-28[29] Score interpretation: 0-7-no clinically significant insomnia 8-14-subthreshold insomnia 15-21-clinical insomnia (moderate severity) 22-28-clinical insomnia (severe)	Responder - 7 point decrease in score from baseline[30] Remitter - achieve total score below 8 at endpoint[29]
Pittsburgh Sleep Quality Index	7 components; 19 items; range 0-21 with higher scores indicating better sleep[29]	Remitter - total score below 5 at endpoint[31]
Sleep Outcomes -		
Sleep onset latency	Minutes	≤30 minutes at endpoint[31] ↓ 50% from baseline[31]
Wake-time after sleep onset	Minutes	≤30 minutes at endpoint[31]
Total sleep time	Minutes	None identified
Sleep efficiency	% (total sleep time/time in bed)	>80 at endpoint[32]
Sleep quality	Subjective assessment using a variety of questions typically rated on a Likert scale.	None identified

ISI=Insomnia Severity Index; MID=minimum important difference; PSQI=Pittsburgh Sleep Quality Index

The overall strength of evidence for primary outcomes within each comparison was evaluated based on five required domains: 1) study limitations (risk of bias); 2) directness (single, direct link between intervention and outcome); 3) consistency (similarity of effect direction and size); 4) precision (degree of certainty around an estimate); and 5) reporting bias.[33] Based on study design and conduct, study limitations were rated low, medium, or high based upon the number of limitations detected during risk of bias assessments. Consistency was rated as consistent, inconsistent, or unknown (e.g., single study) after comparing the direction and size of the effect across studies. Directness was rated direct or indirect depending upon whether the outcome measured had a direct link to patient wellbeing and if comparisons were direct. Precision was rated precise or imprecise based upon whether confidence intervals contain or

exceed clinical differences. Reporting bias was rated as undetected or suspected after assessing the presence of publication bias (i.e., conforming methods and results), selective outcome reporting bias, and selective analysis bias. These were assessed by reviewing the study methodology for outcomes measured and/or analyses planned and not reported; reviewing methods sections for analyses reported but not planned; assessing the grey literature for registered trials without publications. Other factors considered in assessing strength of evidence included dose-response relationship, the presence of confounders, and strength of association. Based on these factors, the overall strength of evidence for each outcome was rated as:[33]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings are likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence is necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Applicability of studies was determined according to the PICOTS framework. Study characteristics affecting applicability include, but are not limited to, the population from which the study participants are enrolled (i.e., studies enrolling participants from sleep medicine clinics may not produce results applicable to the general population of patients being treated for insomnia in primary care clinics), narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies of insomnia.[34] Specific factors that could modify the effect of treatment and affect applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics such as age.

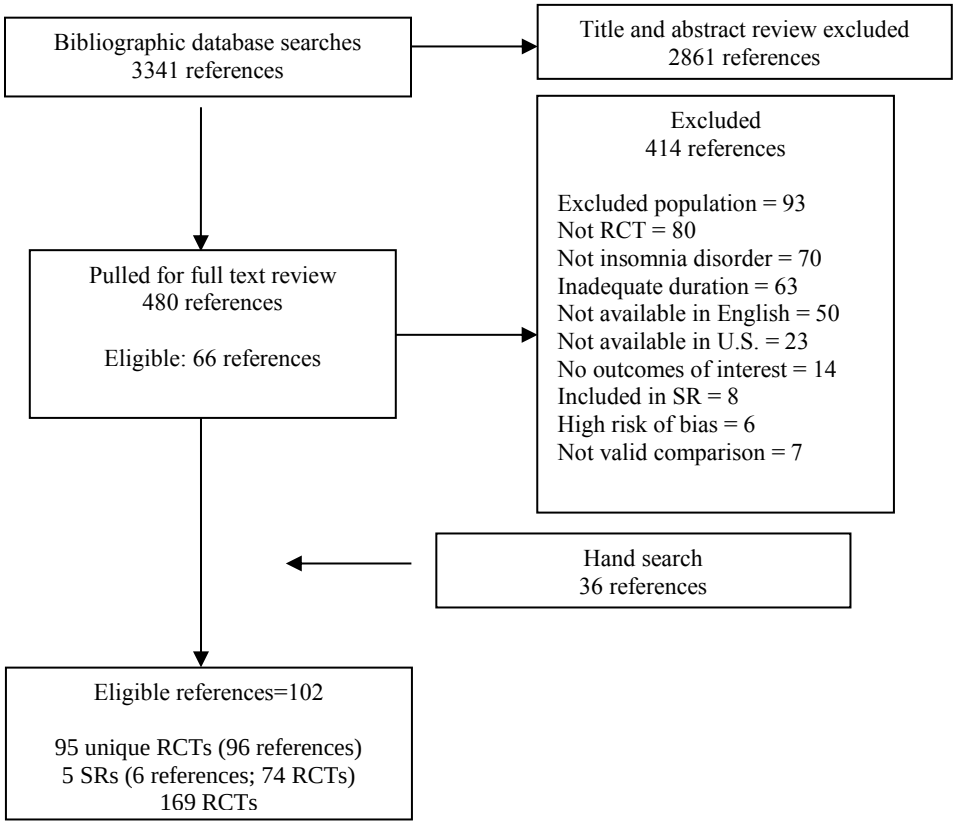
Results

Key Points

- Global outcomes were less often measured than sleep outcomes, especially in the drug studies; recent research was more likely to assess global outcomes.
- Minimum important differences were identified for some instruments used to assess global outcomes, but these were not frequently used nor is it clear whether they are well established. We did not identify established minimum important differences for most sleep outcomes. Remission defined using sleep onset latency and sleep efficiency were the exceptions.
- A large body of literature tests a wide variety of treatments for insomnia disorder. Strength of evidence suffers because of limited studies with similar comparisons, and sample sizes were typically small. Older studies often did not provide data sufficient for analysis.
- Studied pharmacologic and psychological interventions improve short-term measures of insomnia in selected populations-effect sizes vary and a large placebo response is often observed. Broader applicability, comparative effectiveness, long-term efficacy, and harms are less well known.

Our search identified 3341 citations, of which 480 required full text review after title and abstract screening (Figure A). Of the 480 full text articles screened, we identified 66 eligible references; we identified another 36 eligible reference by hand searching for a total of 102 publications of 95 unique RCTs and 5 unique systematic reviews. Systematic reviews included in our analysis synthesized evidence on 74 unique RCTs. The total number of RCTs reflected in this review is 169.

Figure A. Literature flow diagram



Efficacy, Comparative Effectiveness, and Adverse Effects of Psychological Interventions

Key Points

- The efficacy of CBT-I across several delivery modes in the general adult population is well studied; low to moderate strength evidence shows that it improves global outcomes by minimum important differences; moderate strength evidence shows that global outcomes are statistically significantly better with CBT-I than passive control; low to moderate-strength evidence shows that sleep outcomes are improved; however, improvements in sleep outcomes are relatively modest.
- Evidence of CBT-I's efficacy in older adults was insufficient to assess minimum important differences in global outcomes; evidence was insufficient to assess sleep onset latency and total sleep time; moderate-strength evidence shows that CBT decreases wake time after sleep onset by nearly 50 minutes and improves sleep efficiency by 12 points. Low-strength evidence shows that sleep efficiency improved by over 12 percentage points.
- Evidence on the efficacy of multicomponent behavioral treatment in the general adult population was limited. Low strength evidence shows that sleep onset latency improved; evidence for all other outcomes and adverse effects were insufficient.

- Evidence on the efficacy of multicomponent behavioral treatment or BBT in older adults was more robust; low strength evidence shows that global outcomes were improved statistically; moderate strength evidence showed that sleep onset latency, wake time after sleep onset, and sleep efficiency were improved with multicomponent behavioral treatment or BBT; improvements in sleep outcomes were modest.
- Evidence on the efficacy specific behavioral interventions alone (stimulus control, sleep restriction, relaxation techniques) was limited; sufficient evidence was available for few outcomes:
    - Moderate-strength evidence shows that sleep restriction decreased wake time after sleep onset in older adults; low-strength evidence showed no statistically significant improvement in total sleep time; evidence for all other outcomes was insufficient.
    - Low-strength evidence shows that stimulus control improves total sleep time in the general adult population and older adults. Low strength evidence shows that wake time after sleep onset with no different from passive control in the general adult population. Evidence for all other outcomes was insufficient.
    - Low-strength evidence shows that relaxation techniques decrease sleep onset latency in the general adult population; evidence for all other outcomes was insufficient.
    - Evidence comparing different psychological interventions was insufficient to conclude that any one treatment is more efficacious than another.

We identified 51 RCTs of psychological interventions and grouped them based on intervention type and comparison. Interventions that had both cognitive and behavioral components were grouped into a CBT category. Interventions with multiple behavioral components without a cognitive component were grouped with multicomponent behavioral or brief behavioral therapy. Single interventions became groups of their own. The more commonly studied single-therapy interventions included sleep restriction/sleep compression, stimulus control, and progressive relaxation. Less commonly used single-therapy interventions included biofeedback/neurofeedback, light therapy, and exercise. Studies of psychological interventions typically enrolled adults with insomnia disorder lasting years. Participants often had comorbidities and could be on medications. Table C lists global and sleep outcomes for all psychological interventions in the general adult population. Table D lists global and sleep outcomes for all psychological interventions in older adults. Secondary outcomes are discussed in the main report.

Evidence from 17 RCTs (n=1,878) demonstrates that CBT is an effective treatment for insomnia disorder.[35] Effectiveness was demonstrated across modes of delivery (individual in-person, in-person group, telephone, Web-based, self-help book-based) for both global and sleep outcomes. Four studies (n=115) assessed remission from insomnia using two different instruments (ISI and PSQI). The difference in improvement in global outcomes exceeded that of passive controls (waitlist, no treatment, and/or information) by more than the established minimum important difference (established for a change from baseline). CBT efficacy trials demonstrated improvements across all five sleep outcomes according to data pooled from 11 to 13 studies per outcome representing 734 to 1091 participants. Pooled estimates showed that CBT resulted in reduced sleep onset latency of 11 minutes, increased total sleep time of 11 minutes, reduced wake time after sleep onset of 26 minutes, improved sleep efficiency by more than 6 percentage points, and a moderately sized improvement in sleep quality. Adverse effects of CBT were not often reported. Withdrawals were reported in some studies, but data was insufficient to assess differences in adverse effects by group.

Two small RCTs (n=50) evaluated multicomponent behavioral therapies in the general adult population. No global outcomes were reported. Data was sufficient to assess only one sleep outcome, sleep onset latency. BBT was associated with a decrease of 23 minutes compared with passive controls. Neither trial reported specific adverse effects. Data was insufficient to assess differences in withdrawals.

Five trials (n=194) assessed the efficacy of stimulus control alone. Most had small sample sizes. Few reported similar outcomes or data that could be pooled. Data was sufficient for only one outcome, total sleep time. Stimulus control was associated with a 43 minute increase in total sleep time compared with passive controls. Studies did not report specific adverse effects. Two studies reported withdrawals by group which provided insufficient data to assess a difference.

Table C. Efficacy and comparative effectiveness of psychological interventions for insomnia disorder in the general adult population

Psychological Intervention	Improves Global Outcomes (MID) SOE	Improves Global Outcomes (Statistical) SOE	Sleep Outcomes—Sleep Onset Latency WMD Minutes [95% CI] SOE	Sleep Outcomes—Total Sleep Time, WMD Minutes [95% CI] SOE	Sleep Outcomes—Wake After Sleep Onset, WMD Minutes [95% CI] SOE	Sleep Outcomes—Sleep Efficiency, WMD, Percentage Points [95% CI] SOE	Sleep Outcomes—Sleep Quality, SMD [95% CI] SOE	Increased Adverse Effects SOE
Efficacy								
CBT	√ Moderate	√ Moderate	-11.3 [-18.0 to -4.7] Moderate	11.2 [1.5 to 21.0] Moderate	-26.4 [-41.0 to -11.8] Moderate	6.1 [3.2 to 9.0] Moderate	0.43[a] [0.2 to 0.6] Moderate	Insufficient
Multi-component Behavioral Therapy or BBT	NR	NR	-23.4 [-36.3 to -9.9] Low	Insufficient	Insufficient			
Stimulus control	NR	NR	Insufficient	43.2 [3.3 to 83.1] Low	Insufficient	Insufficient	Insufficient	Insufficient
Relaxation	NR	NR	-38.65 [-73.61 to -3.69] Low	Insufficient	NR	NR	NR	NR
Comparative Effectiveness								
Stimulus control vs. relaxation	NR	NR	Insufficient	Insufficient	NR	NR	NR	NR

√=improvement; BBT-brief behavioral therapy; CBT=cognitive behavioral therapy; CI=confidence interval; MID=minimum important difference; NR= not reported; SC=stimulus control; SMD=standardized mean difference; SOE=strength of evidence; WMD=weighted mean difference

[a] Indicates moderate effect size

Table D. Efficacy and comparative effectiveness of psychological interventions for insomnia disorder in older adults

Psychological Intervention	Improves Global Outcomes (MID)	Improves Global Outcomes (Statistical)	Sleep Outcomes—Sleep Onset Latency WMD Minutes [95% CI] SOE	Sleep Outcomes—Total Sleep Time, WMD Minutes [95% CI] SOE	Sleep Outcomes—Wake After Sleep Onset, WMD Minutes [95% CI] SOE	Sleep Outcomes—Sleep Efficiency, WMD, Percentage Points [95% CI] SOE	Sleep Outcomes—Sleep Quality, SMD [95% CI] SOE	Increased Adverse Effects SOE
Efficacy								
CBT-I	Unclear Insufficient	√ Moderate	Insufficient	Insufficient	-48.3 [-78.9 to -17.8] Moderate	12.4 [7.6 to 17.3] Low	NR	Insufficient
BBT	Insufficient	√ Low	-10.36 [-15.57 to -5.15] Moderate	NS Low	-13.9 [-21.1 to -6.7] Moderate	5.1 [2.5 to 7.8] Moderate	Insufficient	Insufficient
Sleep restriction	Insufficient	Insufficient	Insufficient	Insufficient	WMD= -24.47 [-40.98 to -7.96] Moderate	Insufficient	Insufficient	Insufficient
Stimulus control	Insufficient	Insufficient	Insufficient	40.37 [23.47 to 57.27] Low	Insufficient	Insufficient	Insufficient	Insufficient

√=improvement; BBT=brief behavioral therapy; CBT-I=cognitive behavioral therapy; CI=confidence interval; MID=minimum important difference; NR=not reported; NS=no statistical difference between groups; SMD=standardized mean difference; SOE=strength of evidence; WMD=weighted mean difference.

Two RCTs (n=42) studied the efficacy of progressive relaxation or other forms of relaxation in the general adult population. No study reported global outcomes; data was sufficient only for sleep onset latency. Relaxation was associated with decreased sleep onset latency of nearly 40 minutes.

Two RCTs (n=62) compared relaxation to stimulus control. Stimulus controls appears to decrease sleep onset latency more than relaxation.

Four trials studied the efficacy of CBT-I in older adults. We could not determine whether improvements surpassed minimum important differences since no threshold score change indicating response to treatment was available for the instrument used (PSQI). Global outcomes were statistically significantly better in the CBT-I participants than passive controls. Evidence was insufficient to assess sleep onset latency and total sleep time, but wake time after sleep onset and sleep efficiency were better after CBT-I. Evidence was insufficient to assess adverse effects.

Four RCTs (n=181) studied the efficacy of multicomponent behavioral treatments or brief behavioral treatment in older adults. The bulk of the evidence comes from one larger BBT trial; global and sleep outcomes from three smaller trials of multicomponent behavioral treatments were consistent in direction and magnitude of effect. Evidence was insufficient on all other outcomes and adverse effects.

Three RCTs (n=171) studied the efficacy of sleep restriction in older adults. Sleep restriction improved global outcomes and improved wake time after sleep onset. Evidence was insufficient for other sleep outcomes and adverse effects.

Three RCTs (n=129) studied the efficacy of group or in-person stimulus control in older adults. Stimulus control improved the rate at which older adults remitted from insomnia. Total sleep time improved by 40 minutes over passive control with stimulus control. Evidence was insufficient for sleep onset latency and adverse effects.

Efficacy, Comparative Effectiveness, and Adverse Effects of Pharmacologic Interventions

Key Points

- Nonbenzodiazepine hypnotics have low to moderate strength evidence for efficacy on global and a wide range of sleep outcomes in the general adult population. Improvements over placebo in sleep outcomes were higher with eszopiclone and zolpidem than zaleplon. Results for adverse effects were mixed with few differences compared to placebo.
- Eszopiclone and zolpidem had some evidence of improved outcomes in older adults. Low strength evidence shows that eszopiclone improved one global outcome by a minimum important difference and improved several sleep outcomes, but not sleep onset latency. Evidence on adverse effects was insufficient. Low strength evidence shows that zolpidem improved sleep onset latency had higher adverse effects. Evidence on other outcomes was insufficient.
- Prolonged release melatonin improved one sleep outcome in the general adult population; low strength evidence shows that sleep onset latency improved by a mean of 6 minutes; evidence for all other outcomes and adverse effects were insufficient.
- Ramelteon was similar to placebo with respect to three sleep outcomes in the general adult population. There was no difference in sleep onset latency, total sleep time, or wake time after sleep onset. Low strength evidence shows that sleep quality improved less with

ramelteon than with placebo. Withdrawals were higher with ramelteon (low strength evidence), but withdrawals for adverse effects and number of patients with more than one adverse effect were similar in both groups (low and moderate strength evidence, respectively).

- Low strength evidences shows ramelteon was similar to placebo with respect to two sleep outcomes in older adults, but did improve sleep onset latency by an average of 6 minutes. Low strength evidence shows no difference in adverse effects between ramelteon and placebo.
- Very few benzodiazepine trials met eligibility criteria. Data was insufficient to assess any global, sleep, or adverse effect outcomes in the general adult or older adult populations.
- Data on antidepressants (trazodone and doxepin) in the general adult population was insufficient for global and sleep outcomes. No differences in proportion of participants in the doxepin trial with more than one adverse effect were demonstrated. Evidence was insufficient for other adverse effects.
- Data on antidepressants (doxepin) in older adults was insufficient for global and sleep outcomes. Low strength evidence shows no differences in adverse effects.
- Few eligible trials studied the comparative effectiveness of different drugs in treating insomnia. One comparison had sufficient evidence for one sleep outcome. Zolpidem and zaleplon achieved similar levels of sleep quality (moderate strength of evidence) and has similar levels of adverse effects (low strength of evidence).

We identified 32 RCTs that evaluated pharmacologic treatments for insomnia disorder in the general adult population (Table E) and in older adults (Table F). We found the most data on the newer FDA-approved drugs.

Nonbenzodiazepine hypnotics have the strongest evidence of efficacy in the general adult population. Fourteen RCTs studied nonbenzodiazepine hypnotics in the general adult population - eszopiclone (3 RCTs; n=1,929); zaleplon (2 RCTs; n=973); zolpidem (4 RCTs; n=704); zolpidem 'as needed' (3 RCTs; n=1,929); zolpidem SL (1 RCT; n=295); zolpidem ER (1 RCT; n=1,018). Only eszopiclone, zolpidem 'as needed', and zolpidem ER reported global outcomes. All three improved global outcomes and eszopiclone and zolpidem 'as needed' led to the decreases in sleep onset latency and increases in total sleep time. Zolpidem and zaleplon improved two sleep outcomes – sleep onset latency and sleep quality (low to moderate strength evidence). However, neither drug improved total sleep time (low strength evidence). Results for adverse effects varied across the different drugs and typically were not different from placebo. Adverse effects reported did not appear serious and included somnolence, unpleasant taste, and myalgia with eszopiclone, and somnolence with zolpidem.

Fewer trials assessed nonbenzodiazepine hypnotics for in older adults with insomnia (Table F). Those that enrolled only older adults randomized participants to low doses of the drug. Evidence was insufficient to assess efficacy in older adults for eszopiclone, 2 mg, (1 RCT; n=388) and zolpidem, 5 mg (1 RCT; n=166).

Seven RCTS studied melatonin and melatonin agonists in the general adult population. One studied melatonin PR (n=711) and five studied ramelteon (n=3,124). Evidence was insufficient on most melatonin PR outcomes. Low strength evidence shows that sleep onset latency improved by a mean of 6 minutes and no differences in the proportion of participants reporting more than one adverse effect.

One RCT (n=829) studied the efficacy of ramelteon in older adults. No global outcomes were reported. Sleep onset latency improved by a mean of 10 minutes, but there were no differences over placebo in total sleep time, sleep quality, or adverse effects.

Few benzodiazepine or antidepressant trials met eligibility criteria, primarily due to short treatment durations. Evidence on temazepam, triazolam, flurazepam, and quazepam was insufficient for global, sleep, and adverse effect outcomes in the general and older adult populations. Evidence on doxepin in the general adult population was insufficient to assess global, sleep, and adverse effect outcomes. Only adverse effects for doxepin had sufficient evidence in the older adult populations, showing no difference in withdrawals, withdrawals due to adverse effects, or the proportion of participants reporting more than one adverse effect.

Few eligible trials studied the comparative effectiveness of different drugs in treating insomnia. On study comparing zolpidem to temazepam provided insufficient evidence for all global, sleep, and adverse effect outcomes. One comparison had sufficient evidence for one sleep outcome. Zolpidem and zaleplon achieved similar levels of sleep quality (low strength of evidence) and has similar levels of adverse effects (low strength of evidence).

Table E. Efficacy and comparative effectiveness of pharmacologic interventions for insomnia disorder in the general adult population

Pharmacological Intervention	Improves Global Outcomes (MID) SOE	Improves Global Outcomes (Statistical) SOE	Sleep Outcomes—Sleep Onset Latency WMD Minutes [95% CI] SOE	Sleep Outcomes—Total Sleep Time, WMD Minutes [95% CI] SOE	Sleep Outcomes—Wake After Sleep Onset, WMD Minutes [95% CI] SOE	Sleep Outcomes—Sleep Efficiency, WMD, Percentage Points [95% CI] SOE	Sleep Outcomes—Improved Sleep Quality, SMD [95 % CI] or RR [95% CI] SOE	Increased Adverse Effects SOE
Efficacy Nonbenzo-diazepine hypnotics								
Eszopiclone, 2 or 3 mg	√ Low	√ Low	-19.1 [-24.1 to -14.1] Low	44.8 [35.4 to 54.2] Low	-10.8 [-19.8 to -1.70] Low	NR	SMD 0.47 [0.32 to 0.61] Low	Mixed results Insufficient to Low
Zaleplon, 5, 10 or 20 mg	Insufficien t	Insufficient	Insufficient	NS Low	NR	NR	RR 1.19 [1.02 to 1.38] Moderate	NS Low to Moderate
Zolpidem, 10 or 15 mg	NR	NR	-12.8 [-21.5 to -4.2] Moderate	NS Low	NR	NR	RR 1.40 [1.20 to 1.65]Moderate	Mixed results Low-Moderate
Zolpidem, 10 mg as needed	√ Low	√ Low	-14.8 [-23.4 to -6.2] Moderate	48.1 [34.8 to 61.5] Moderate	NS Low	NR	NR	NS Insufficient to Low
Zolpidem SL	NR	NR	Insufficient	Insufficient	Insufficient	NR	Insufficient	Insufficient
Zolpidem ER	√ Low	NR	Insufficient	Insufficient	Insufficient	NR	NR	Mixed results Low
Efficacy Melatonin agonists								
Melatonin prolonged release, 2 mg	NR	Insufficient	-6 [-10 to -2.1] Low	NR	NR	NR	Insufficient	Mixed results Insufficient to Low
Ramelteon, 4 to 16 mg			NS Low	NS Low	NS Low	NR	SMD -0.08 [-0.16 to -0.01] Low	Mixed results Low to moderate
Efficacy of Benzodiazepine hypnotics								
Temazepam	NR	NR	Insufficient	Insufficient	NR	Insufficient	NR	NR
Triazolam	NR	NR	Insufficient	Insufficient	NR	NR	NR	Insufficient
Flurazepam	NR	NR	Insufficient	Insufficient	NR	NR	NR	Insufficient
Quazepam	NR	NR	Insufficient	Insufficient	NR	NR	NR	Insufficient

Pharmacological Intervention	Improves Global Outcomes (MID) SOE	Improves Global Outcomes (Statistical) SOE	Sleep Outcomes—Sleep Onset Latency WMD Minutes [95% CI] SOE	Sleep Outcomes—Total Sleep Time, WMD Minutes [95% CI] SOE	Sleep Outcomes—Wake After Sleep Onset, WMD Minutes [95% CI] SOE	Sleep Outcomes—Sleep Efficiency, WMD, Percentage Points [95% CI] SOE	Sleep Outcomes—Improved Sleep Quality, SMD [95 % CI] or RR [95% CI] SOE	Increased Adverse Effects SOE
Efficacy of Antidepressants								
Doxepin, 3, 6, and 25 mg	Insufficient	Insufficient	NR	Insufficient	Insufficient	NR	Insufficient	NS Insufficient to Low
Comparative Effectiveness								
Zolpidem, 10 mg vs. Temazapam, 20 mg	NS Low	NS Low	NS Low	Favors Zolpidem 27.0 [2.1 to 51.9] Low	NS Low	NR	NR	NR
Zolpidem, 10 mg vs. Zaleplon, 10 and 20 mg	NR	NR	Insufficient	Insufficient	NR	NR	RR 0.90 [0.80 to 1.01] Moderate	NS Low to Moderate

√=improvement; CI=confidence interval; MID=minimum important difference; NR= not reported; NS=no statistical difference; SMD=standardized mean difference; SOE=strength of evidence; WMD=weighted mean difference.

Table F. Efficacy and comparative effectiveness of pharmacological interventions for insomnia disorder in older adults

Pharmacological Intervention	Improves Global Outcomes (MID)	Improves Global Outcomes (Statistical)	Sleep Outcomes—Sleep Onset Latency WMD Minutes [95% CI] SOE	Sleep Outcomes—Total Sleep Time, WMD Minutes [95% CI] SOE	Sleep Outcomes—Wake After Sleep Onset, WMD Minutes [95 % CI] SOE	Sleep Outcomes—Sleep Efficiency, WMD, Percentage Points [95% CI] SOE	Sleep Outcomes—Improved Sleep Quality, SMD [95% CI] SOE	Increased Adverse Effects SOE
Efficacy Nonbenzo-diazepine hypnotics								
Eszopiclone, 2 mg	√ Low	√ Low	NS Low	30.0 [19.7 to 40.3] Low	-48.3 [-78.9 to -17.8] Low	12.4 [7.6 to 17.3] Low	0.24 [0.04 to 0.44]Low	Insufficient
Zolpidem, 5 mg	NR	NR	Insufficient	Insufficient	NR	NR	NR	Insufficient
Efficacy Melatonin agonists								
Ramelteon, 4 to 8 mg	NR	NR	-10.1 [-15.6 to -4.6] Low	NS Low	NR	NR	NS Low	NS Low
Efficacy of Benzodiazepine hypnotics								
Temazepam	NR	NR	NR	NR	22.3 [-36.8 to -7.7] Insufficient	9.2 [2.8 to 15.6] Insufficient	NR	Insufficient
Triazolam	NR	NR	Insufficient	Insufficient	NR	NR	Insufficient	Insufficient
Efficacy of Anti-depressants								
Doxepin, 1, 3, and 6 mg	No Low	√ Low	Insufficient	Insufficient	NR	NR	Insufficient	NS Low-Insufficient
Trazadone	Insufficient	Insufficient	NR	NR	NR	NR	NR	Insufficient

√=improvement; CI=confidence interval; MID=minimum important difference; NR= not reported; NS=no statistical difference; SMD=standardized mean difference; SOE=strength of evidence; WMD=weighted mean difference.

Efficacy, Comparative Effectiveness, and Adverse Effects of Complementary and Alternative Interventions

Key Points

- Evidence from three systematic reviews and five RCTs provided insufficient evidence to assess the efficacy or comparative effectiveness of acupuncture, homeapathy, valerian, magnesium, yoga, and passive stretching for insomnia.

We identified three systematic reviews and five RCTs evaluating CAM treatments for insomnia disorder. None of the trials contained similar comparisons. The five RCTs studied wuling capsule, therapeutic massage, yoga, isoflavones, homeopathic complex, and passive stretching. Evidence was insufficient for all comparisons for global, sleep and adverse effect outcomes.

Comparative Effectiveness and Adverse Effects across Intervention Types

Key Points

- A previous fair quality systematic review concluded that CBT-I is effective for treating insomnia when compared with drug treatments and the effects may be more durable than drugs:
  - Moderate strength evidence from three RCTs shows that CBT-I is better than benzodiazapines for long-term treatment of insomnia.
  - Moderate strength evidence from two RCTs shows that CBT-I is better than nonbenzodiazapine hypnotics for short-term treatment of insomnia.
  - Low strength evidence from two RCTs shows that CBT-I is better than nonbenzodiazapine hypnotics for long-term treatment of insomnia.

We identified one systematic review and seven RCTs evaluating the comparative effectiveness across intervention types. Most trials assessed efficacy in the general adult population. The previous systematic review found that CBT-I and drug treatments both improved sleep outcomes; however, CBT-I produced more sustainable results. Evidence was insufficient for all other comparisons.

Discussion

We systematically searched and synthesized the literature on a comprehensive set of interventions for insomnia disorder. Most trials assessed efficacy in the general adult population. We found low to moderate-strength evidence for the efficacy of certain psychological and pharmacologic interventions for some outcomes. Evidence on a variety of CAM interventions was insufficient to assess the efficacy of these interventions.

The strongest evidence for efficacy in the general adult population is for CBT-I across a variety of delivery modes. CBT-I improved global outcomes by minimum important differences when clearly established and otherwise by statistical measures. It also improved all sleep outcomes. Evidence was insufficient to compare CBT-I delivery modes. However, the range of modes available should enhance access to CBT-I. Evidence was not as robust for other

psychological interventions because there were far fewer studies that assessed the same treatment and passive control in similar populations, and sample sizes were typically small. Psychological interventions are noninvasive and assumed to be low-harm interventions, but the studies were not good about recording withdrawals and often reported withdrawals in the overall population as opposed to withdrawals by group. Withdrawals are more likely due to intervention feasibility (i.e., requires too much time) than to physical or psychological harms, but reporting this information would improve understanding the feasibility of these interventions in practice.

We also found low to moderate-strength evidence of efficacy of nonbenzodiazepine hypnotics in the general adult population. These are the most commonly used medications for insomnia. Eszopiclone (Lunesta), zolpidem (Ambien), and zaleplon (Sonata) improved sleep outcomes. Few pharmaceutical trials measured and reported global outcomes; however, low-strength evidence suggests that eszopiclone, 2 and 3 mg, zolpidem 'as needed'improve global outcomes. Eszopiclone and zolpidem achieved larger improvements in sleep outcomes than zaleplon, Results for adverse effects were mixed and often not different from placebo. However, most RCTs had duration shorter than drug therapy is used in practice. It is possible that these RCTs did not capture rare serious adverse effects associated with long-term use.

Evidence for other drug classes was limited. Melatonin PR showed a small improvement in one sleep outcome, but the improvement in sleep onset latency was modest (average decrease of 6 minutes). Low-strength evidence shows that ramelteon did not improve sleep outcomes when compared with placebo. Few efficacy studies of benzodiazepine hypnotics and antidepressants met inclusion criteria. We had few findings for these drugs.

The efficacy of insomnia interventions in older adults is assessed separately because their symptoms tend to differ from those of younger adults. Specifically, compared to younger adults, older adults are more likely to report waking after sleep onset more that sleep onset latency. In addition, older adults are often more sensitive to medications and their side effects, which can more easily become serious. Psychological interventions (CBT-I, BBT, and other multicomponent behavioral interventions) improve global outcomes (but not by minimum important differences) and sleep outcomes in older adults. Evidence is insufficient to assess adverse effects. A very limited number of pharmacologic studies enrolled only older adults. From these, we found low-strength evidence that low doses of eszopiclone and zolpidem improved some sleep outcomes in older adults without significantly different adverse effects from placebo.

Current evidence has several limitations. First, data were limited for specific comparisons, despite having a large number of eligible studies. RCTs of psychological interventions contained a wide variety of intervention and control conditions limiting the data available to analyze similar comparisons. Older psychological studies were often underpowered and did not provide data sufficient for analysis (no group sample sizes, outcomes presented graphically without confidence intervals, etc.). Few trials measured and reported global outcomes. Insomnia disorder requires select sleep symptoms accompanied by daytime dysfunction or distress. Most trials measured only sleep outcomes which may not accurately reflect overall impact. This lack is especially important given the daytime symptoms that often accompany hypnotic drugs. Recent trials are more likely to report global outcomes. Also, we found little evidence establishing and using minimum important differences in this population. Although remission and response have been established for some instruments, they have not been consistently used. Sleep parameters are commonly reported in insomnia efficacy and comparative effectiveness trials. However, the literature contains few established minimum important differences for use in assessing efficacy

and effectiveness. It was not clear how many minutes reduction in sleep onset latency, total sleep time, or wake time after sleep onset indicated clinical improvement. Sleep efficiency and sleep quality provided comprehensive measures of sleep and established minimum important differences or standardized effect size guidance eased interpretation of these measures.

Eligible drug trials rarely lasted longer than 6 weeks. Individuals taking medications for sleep often stay on the medications for months to years. Our review was designed to detect short term adverse effects associated with these drugs. Findings of safety in our review do not rule out the risk of serious adverse events associated with long-term use or rare adverse events. To gain an accurate synthesis of these adverse events would need to collect data from grey literature and observational studies. However, such studies have significant risk of selection bias and confounding. Previous research has summarized these adverse effects. Using pooled analyses of RCT data submitted to the FDA, Kripke et al. found increased incidence of depression[36] and skin cancer[37] among participants using nonbenzodiazepine hypnotics and ramelteon compared with placebo. Carson et al.[39] conducted a systematic review that included observational studies and case reports of nonbenzodiazepine hypnotics. In observational studies lasting 6-months to 1 year, Carson et al. found eszopiclone and zaleplon were associated with mild to moderate adverse effects, while zolpidem was associated with serious adverse effects such as amnesia, vertigo, confusion, and diplopia. A meta-analysis by Glass and colleagues showed that use of sedative–hypnotics in older people with insomnia resulted in a five-fold increase in memory loss, confusion, and disorientation; a three-fold increase in dizziness, loss of balance, or falls; and a four-fold increase in residual morning sedation compared with placebo, though absolute rates may be low.[40]

Future research to improve our understanding of treatments for insomnia disorder should include:

- Conceptual research to establish minimum important differences in sleep outcomes.
- Increased use of global outcomes of insomnia treatment.
- Use of global outcomes definitions that incorporate minimum important differences (remitters and responders).
- Head-to-head comparisons of drugs.
- Drug trials with treatment durations of one year or more, durations adequate to assess efficacy and comparative effectiveness of a chronic condition.
- Systematic review of observational studies to evaluate harms associated with long-term use of medications for insomnia disorder.

References

1. Morin CM, Benca R. Chronic insomnia. Lancet 2012; Mar;379(9821):1129-41. PMID: WOS:000302131800035.
2. Guideline Development Group for the management of patients in primary care. Clinical Practice Guidelines for the Management of Patients with Insomnia in Primary Care; National Health System Quality Plan, Ministry of Health and Social Policy. Health Technology Assessment Unit; Lain Entralgo Agency; . Community of Madrid. 2009.
3. Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep Med Rev 2010; Feb;14(1):69-82. PMID: 19962922.
4. American Psychiatric Association. Sleep-Wake Disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
5. DynaMed [Internet]. Insomnia. EBSCO Information Services. 1995 – Accessed December 5, Registration and login required.
6. Buysse DJ. Insomnia. Jama 2013; Feb 20;309(7):706-16. PMID: 23423416.
7. Xu M, Belanger L, Ivers H, et al. Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. Sleep Med 2011; 12(1):65-9. PMID: 21147026.
8. Rybarczyk B, Lund HG, Garroway AM, et al. Cognitive Behavioral Therapy for Insomnia in Older Adults: Background, Evidence, and Overview of Treatment Protocol. Clinical Gerontologist 2013; Jan;36(1):70-93. PMID: WOS:000312700500005.
9. Montgomery P, Dennis Jane A. Cognitive behavioural interventions for sleep problems in adults aged 60+. John Wiley & Sons, Ltd. 2003. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003161/abstract. Accessed 1.
10. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 2010; Nov;24(11):1577-601. PMID: 20813762.
11. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. Sleep 2006; Nov;29(11):1415-9. PMID: 17162987.
12. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; Oct 15;4(5):487-504. PMID: 18853708.
13. AASM. Personal Communication; 2013.
14. Zhao K. Acupuncture for the treatment of insomnia. Int Rev Neurobiol 2013; 111:217-34. PMID: 24215925.
15. Xie CL, Gu Y, Wang WW, et al. Efficacy and safety of Suanzaoren decoction for primary insomnia: a systematic review of randomized controlled trials. BMC Altern Med 2013; 13:18. PMID: 23336848.
16. Yeung W-F, Chung K-F, Poon MM-K, et al. Prescription of Chinese herbal medicine and selection of acupoints in pattern-based traditional Chinese medicine treatment for insomnia: a systematic review. Evidence-Based Complementary and Alternative Medicine 2012; 2012.
17. Yeung WF, Chung KF, Poon MM, et al. Chinese herbal medicine for insomnia: a systematic review of randomized controlled trials. Sleep Med Rev 2012; Dec;16(6):497-507. PMID: 22440393.
18. Yeung WF, Chung KF, Poon MM, et al. Acupressure, reflexology, and auricular acupressure for insomnia: a systematic review of randomized controlled trials. Sleep Med 2012; Sep;13(8):971-84. PMID: 22841034.
19. Fismer KL, Pilkington K. Lavender and sleep: A systematic review of the evidence. European Journal of Integrative Medicine 2012; Dec;4(4):E436-E47. PMID: WOS:000312093100011.
20. Cheuk DK, Yeung WF, Chung KF, et al. Acupuncture for insomnia. Cochrane Database Syst Rev 2012; 9:CD005472. PMID: 22972087.
21. Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. Sleep Med Rev 2011; Apr;15(2):99-106. PMID: 20965131.
22. Lee J, Han M, Chung Y, et al. Effects of foot reflexology on fatigue, sleep and pain: a systematic review and meta-analysis. Journal Korean acad 2011; Dec;41(6):821-33. PMID: 22310867.
23. Ernst E, Lee MS, Choi TY. Acupuncture for insomnia? An overview of systematic reviews. Eur J Gen Pract 2011; Jun;17(2):116-23. PMID: 21463162.

24. Morin CM. Measuring outcomes in randomized clinical trials of insomnia treatments. Sleep Med Rev 2003; Jun;7(3):263-79. PMID: 12927124.
25. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.2. 2012.
26. White C, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. 2009. http://effectivehealthcare.ahrq.gov/repFiles/methodsguide/systematicreviewsreplacedenovo.pdf.
27. Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. Journal of Clinical Epidemiology 2011.
28. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology 2011; Nov;64(11):1187-97. PMID: 21477993.
29. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res (Hoboken) 2011; Nov;63 Suppl 11:S287-96. PMID: 22588751.
30. Morin CM, Beaulieu-Bonneau S, LeBlanc M, et al. Self-help treatment for insomnia: a randomized controlled trial. Sleep 2005; Oct;28(10):1319-27. PMID: 16295218.
31. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep 2004; Dec 15;27(8):1567-96. PMID: 15683149.
32. Bastien CH, Fortier-Brochu E, Rioux I, et al. Cognitive performance and sleep quality in the elderly suffering from chronic insomnia. Relationship between objective and subjective measures.[Erratum appears in J Psychosom Res. 2003 Nov;55(5):475]. J Psychosom Res 2003; Jan;54(1):39-49. PMID: 12505554.
33. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. 2013.
34. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010 December. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412. Accessed AHRQ Publication No. 11-EHC019-EF.
35. Brasure M. Comparative Effectiveness of Treatments for Insomnia Disorder. 2014.
36. Kripke DF. Greater incidence of depression with hypnotic use than with placebo. BMC Psychiatry 2007; Aug;7. PMID: WOS:000250031000001.
37. Kripke DF. Possibility that certain hypnotics might cause cancer in skin. J Sleep Res 2008; Sep;17(3):245-50. PMID: 18844818.
38. Sidani S, Epstein DR, Bootzin RR, et al. Assessment of preferences for treatment: validation of a measure. Res Nurs Health 2009; Aug;32(4):419-31. PMID: 19434647.
39. Carson S, McDonagh M, Thakurta S. Drug Class Review: Newer Drugs for Insomnia: Final Report Update 2 [Internet]. Portland (OR): Oregon Health & Science University (www.ncbi.nlm.nih.gov/books/NBK47207) 2008.
40. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. Bmj 2005; Nov 19;331(7526):1169. PMID: 16284208.

Introduction

Background

Sleep problems are some of the most common complaints for adults in primary care.[1] They are associated with a decline in overall health status and perception of poor health and can have negative personal and social consequences.[2]

The term insomnia is variously defined and can describe a symptom and/or a disorder. It involves dissatisfaction with sleep quantity or quality and is associated with one or more of the following subjective complaint(s): difficulty with sleep initiation, difficulty maintaining sleep, or early morning waking with inability to return to sleep.[3] Individuals with sleep problems also report higher levels of anxiety, physical pain and discomfort, and cognitive deficiencies.[4] Insomnia may be associated with long-term health consequences, including increased morbidity, respiratory disease, rheumatic disease, cardiovascular disease, cerebrovascular conditions, and diabetes.[2]

Annual cost estimates for insomnia in the United States range from $30 – $107 billion.[5] Direct costs of $12 – $14 billion cover expenses such as medical appointments, over-the-counter sleep aids, and prescription medication. The remainder includes indirect costs such as lost productivity due to absenteeism and presenteeism (attending work while sick, fatigued), reduced quality of life, accidents, and injuries.

Insomnia disorder should be diagnosed using diagnostic criteria from the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) and/or the International Classification of Sleep Disorders (ICSD). Both have been recently updated. The fifth edition of the DSM (DSM-5)[3] is geared towards primary care and general mental health providers. Its criteria for an insomnia disorder diagnosis require that sleep symptoms cause clinically significant distress or impairment(s) in functioning (social, occupational, educational, academic, behavioral, or other) and occur despite adequate opportunity for sleep on at least three nights per week for at least three months. Diagnosis also requires that symptoms not be primarily linked to other sleep disorders or occur exclusively during the course of another sleep-wake disorder (narcolepsy, breathing-related sleep disorder, circadian rhythm disorder); not be attributable to the physiological effects of a substance; and not be explained by coexisting mental disorders or medical conditions. Dysfunction associated with insomnia disorder includes fatigue, poor cognitive function, mood disturbance, and distress or interference with personal functioning.[1,6] Both criteria recognize sleep-related complaint(s) despite adequate opportunity for sleep combined with distress or dysfunction created by the sleep difficulty in their current and previous versions. Until recently, diagnostic criteria classified insomnia as primary or comorbid, depending on the absence or presence of other conditions. However, both the DSM-5 and the ICSD-III now use the term "insomnia disorder" and eliminate the distinction between primary and comorbid insomnia.[3] The distinction had questionable relevance in clinical practice, and revisions reflect this understanding by suggesting a diagnosis of insomnia disorder for patients who meet diagnostic criteria, despite any coexisting conditions, unless the other condition explains the sleep problems.

Depending on how insomnia is defined, prevalence estimates range from nearly 33 percent in an international sample of primary care patients to 17 percent of U.S. adults reporting "regularly having insomnia or trouble sleeping in the past 12 months" to 6 – 10 percent of adults meeting established diagnostic criteria.[1,3,6,7] Insomnia disorder in the general population consists of difficulties getting to sleep and maintaining sleep.[8] Previous diagnostic criteria for insomnia did

not specify a minimum timeframe for sleep difficulties; chronic insomnia was used to describe cases that lasted from weeks to months, and insomnia was considered chronic in 40 – 70 percent of cases.[6]

Women are 1.4 times more likely than men to suffer from insomnia.[9] Older adults also have higher prevalence of insomnia; aging is often accompanied by changes in sleep patterns (disrupted sleep, frequent waking, early waking) that can lead to insomnia.[10] Older adults typically report difficulty maintaining sleep.[8] Many insomnia cases coexist with a psychiatric diagnosis;[11] however, current diagnostic criteria suggest that insomnia disorder includes sleep problems that cannot be explained by another mental or medical condition.

Individuals suffering from sleep problems tend to seek treatment when symptoms become bothersome (e.g., distress, fatigue, daytime functioning, cognitive impairment).[5] Once insomnia disorder is accurately diagnosed, many treatments are available (Table 1), including over-the-counter medications and supplements, education on sleep hygiene and recommended lifestyle changes, behavioral and psychological interventions, prescription medications, and complementary and alternative medicine (CAM) treatments.

Current guidelines also stress the importance of identifying and treating coexisting conditions. Various treatment options described in the guidelines include psychological and behavioral interventions, drugs, and combined approaches.[12] AASM practice parameters state that psychological and behavioral interventions are effective and recommended for primary chronic insomnia and secondary insomnia (ICSD-II criteria) in adults.[13] Recommendations were supported by the highest quality evidence.[12] Support for short-term use of pharmacological interventions was based on consensus.[12] However, an updated review of evidence synthesis and recommendations on these interventions is underway.[14] Combined or stepped care interventions are also used in treatment. Combination therapy specifies the timing of certain intervention components.[15] The stepped care model has been described in terms of how limited cognitive behavioral therapies (CBT-I) could be used.[16] These approaches are designed to maximize treatment benefits and minimize harms while assisting in efficient delivery of services at the level appropriate for the patient.

Psychological interventions include multicomponent interventions such as CBT-I or brief behavioral therapy (BBT) or single-component treatments such as stimulus control alone, progressive relaxation alone, or sleep restriction alone (Table 2).

Table 1: Examples of treatments for insomnia in adults studied in the literature

Treatment Category	**Treatment**
Psychological	Sleep hygiene education Sleep restriction/sleep compression Stimulus control Brief behavioral therapy (BBT) Cognitive behavioral therapy (CBT)
Complementary and Alternative Medicine (CAM)	Acupuncture Acupressure Cupping Homeopathy Hypnotherapy Reflexology Tai Chi Yoga Herbal/dietary supplements Bach Flower • Isoflavones • L-tryptophan • Magnesium • Melatonin • Valerian
Miscellaneous	Aroma therapy Bright light Exercise Music therapy
Medications[6]	*Generic name*
Medications - antihistamines	Diphenhydramine Doxylamine
Medications - Prescription antidepressants	Amitriptyline Doxepin[a] Trazodone Mirtazapine
Medications – Prescription antipsychotics	Olanzapine Quetiapine
Medications –Prescription hypnotics	<u>Benzodiazepines</u> Alprazolam Clonazepam Estazolam[a] Flurazepam[a] Lorazepam Quazepam[a] Temazepam[a] Triazolam[a] <u>Nonbenzodiazepines</u> Eszopiclone[a] Zaleplon[a] Zolpidem[a]
Medications - melatonin receptor agonist	Melatonin Ramelteon[a]
Medications – Prescription antipsychotics	Gabapentin Pregabalin

[a] FDA approved to treat insomnia

Table 2. Psychological/behavioral interventions for insomnia disorder

Psychological and Behavioral Treatments for Insomnia	Definition
Sleep hygiene education	Behavioral intervention aiming to educate patients about health and environmental factors they can change to improve sleep.
Stimulus control	Behavioral treatment that aims to change behaviors associated with bed and bedroom and establish consistency in sleep patterns.
Sleep restriction	Behavioral intervention that limits time in bed to sleep time, gradually increasing as sleep efficiency improves.
Relaxation training	Training to reduce somatic tension and control bedtime thought patterns that impair sleep.
Cognitive behavior therapy	Combination treatments that include cognitive and behavioral components.
Multicomponent therapy (i.e., Brief Behavioral Treatment)	Multicomponent behavioral therapies without cognitive therapy
Paradoxical intention	Instructing the patients to remain awake and avoid asleep, eliminating performance anxiety.
Biofeedback	Providing visual or auditory feedback to assist them in controlling tension and arousal.
Imagery training	Visualization techniques focusing on pleasant or neutral images to block out thoughts that impair sleep.

Adapted from Morgenthaler T, Kramer M, Alessi C, et al.[13]

Insomnia is often treated with prescription medication. Several prescribed medications are FDA approved (doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon). Several other prescription medications from various drug classes (e.g., antidepressants, antipsychotics) are used off-label.

Efficacy research has also been conducted on a variety of CAM approaches (Chinese herbal medicine, acupuncture, reflexology, Suanzaoren decoction, etc.). Unfortunately, methodological limitations have prevented conclusive evidence synthesis for these treatments.[17-26]

Insomnia treatment goals include meaningful improvements in sleep and associated distress and/or dysfunction. Insomnia treatment may affect several types of outcomes. Global outcomes measure improvements in sleep and the accompanying daytime dysfunction or distress. Sleep outcomes measure specific elements of sleep. Secondary outcomes such as daytime fatigue or sleepiness, mood, or quality of life reflect improvements that reduced symptoms and severity may produce.

Global outcomes are typically measured using questionnaires that contain items assessing sleep and daytime functioning and distress. Unfortunately, many currently available sleep outcome questionnaires were developed to identify poor sleepers and are not adequately sensitive to detect clinically meaningful treatment effects.[27] Two commonly used questionnaires that measure both constructs include the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Index (ISI).

Sleep outcomes, the most frequently reported outcomes in insomnia disorder treatment literature, include sleep-onset latency, number of awakenings, wake time after sleep onset, and total sleep time, and a more comprehensive sleep measure, sleep efficiency (total sleep time/total time in bed). Improvements in these specific sleep measures can be measured objectively or subjectively. Sleep parameters are objectively measured with polysomnography (measuring sleep continuity parameters, sleep time spent in each stage) or actigraphy (measuring body movements). Despite discrepancies between objective and subjective measures of sleep parameters, subjective measures are considered more valuable because they are considered patient-centered outcomes. Sleep quality, subjectively measured in a variety of ways, is also an important measure.

Insomnia treatments can also improve secondary patient-centered outcomes such as mood and well-being, quality of life, and productivity. Questionnaires that measure these outcomes have been used in insomnia efficacy and comparative effectiveness research (i.e., Short-form Health Survey;[SF-36][12,28] Sickness Impact Profile Scale;[28] and World Health Organization Quality of Life [WHOQOL].[28])

Several systematic reviews have assessed the efficacy and comparative effectiveness of insomnia treatment. Available reviews, however, do not incorporate the broad range of interventions (psychological and behavioral, pharmacologic, CAM) or target guideline developers with the specific intention of improving the treatment of insomnia disorder in primary care and general mental health settings. This review identifies previous systematic reviews and randomized controlled trials (RCTs) to provide a comprehensive up-to-date synthesis of the evidence on efficacy and comparative effectiveness of insomnia disorder treatments.

Scope and Key Questions

Preliminary Key Questions for this review were posted for public comment in October 2013. We received several comments useful in revising the Key Questions to better address stakeholder concerns in the most meaningful and efficient way.

Public comments suggested possible contamination by including studies that enroll patients with insomnia as well as other conditions. However, we believe that studies enrolling subjects with the wide variety of conditions (heart disease, diabetes, anxiety/depression, and other chronic medical or psychiatric conditions) accurately reflect the patient population; thus we included these. However, we excluded studies that strictly enroll subjects with a diagnosis that could explain the sleep problems, such as Parkinson's disease or post-traumatic stress disorder.

Public comments also expressed concern over the subjective nature of many outcomes and their associated measurement instruments. While patient-reported outcomes have disadvantages, they are considered patient-centered and thus the best way to assess improvements in response to treatment. By examining the marginal improvement over appropriate control conditions, we hope to better capture the patient's perceived treatment effect.

Key Question 1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

a. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in specific subgroups of adults?
b. What are the efficacy and comparative effectiveness of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for the treatment of insomnia disorder in adults?
c. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

Key Question 2. What are the harms of treatments for insomnia disorder in adults?

a. What are the harms of treatments for insomnia disorder in specific subgroups of adults?
b. What are the harms of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for insomnia disorder in adults?
c. What are the long-term harms of treatments for insomnia disorder in adults?

PICOTS

Population(s)

- Adults, age 18 and above, with insomnia disorder (i.e., insomnia definitions that match insomnia disorder diagnostic criteria)
    - Specific subgroups:
    - older adults (trials that exclusively enroll adults age 55 and older)
    - adults with coexisting medical or mental health disorders (such as mild depression/anxiety)

Intervention Categories (Table 1 lists examples of specific interventions in each category)

- Behavioral/psychological
- CAM
- CAM-herbs and supplements
- Pharmaceutical (available in the United States)
- Other

Comparators

- Drug and CAM supplement efficacy trials must be double-blind placebo controlled. Psychological therapy efficacy trials can be controlled with usual care (i.e., sleep hygiene or sleep education) or wait-list controls; other insomnia treatment. Comparative effectiveness trials can include any active therapy approved and available in the United States.

Outcomes

- KQ1
    - Global outcomes
    - Measures that assess patients' reported improvement in both sleep and daytime functioning or distress associated with sleep symptoms.
      Measurement: Questionnaires that include items related to sleep problems and daytime functioning or distress [i.e., Insomnia Severity Index (ISI);[12,28] Pittsburgh Sleep Quality Index (PSQI);[13,28] Patient Global Impression (PGI) scale.
    - Sleep outcomes, patient-reported
    - Assessments derived from sleep diaries (sleep-onset latency, wake time after sleep onset, total sleep time, sleep efficiency [total sleep time/total time in bed], and sleep quality (variously defined).
    - Secondary patient-centered outcomes
    - Mood/well-being and Quality of life
      Measurement: Assessments derived from questionnaires: [i.e., Beck Depression Inventory (BDI);[12,28] State-Trait Anxiety Inventory (STAI);[12,28] Short-form Health Survey (SF-36);[12,28] World Health Organization Quality of Life (WHOQOL);[28]]; Epworth sleepiness scale (ESS);[12] Fatigue Severity Scale (FSS).[12,28]]
- KQ2
    - Adverse effects of intervention(s)
    - Any adverse effects (e.g., headache, somnolence, myalgia, poor taste, dependence, falls, abnormal sleep behaviors, etc.). Timing for adverse effects will be similar to that of other outcomes (see Timing).

Timing

- KQ1: Outcomes measured at 4 weeks to 3 months after initiation of treatment will be used to assess efficacy/comparative effectiveness.
- KQ1c. Followup measures beyond 3 months of treatment will be used to evaluate long-term efficacy and comparative effectiveness.

Settings

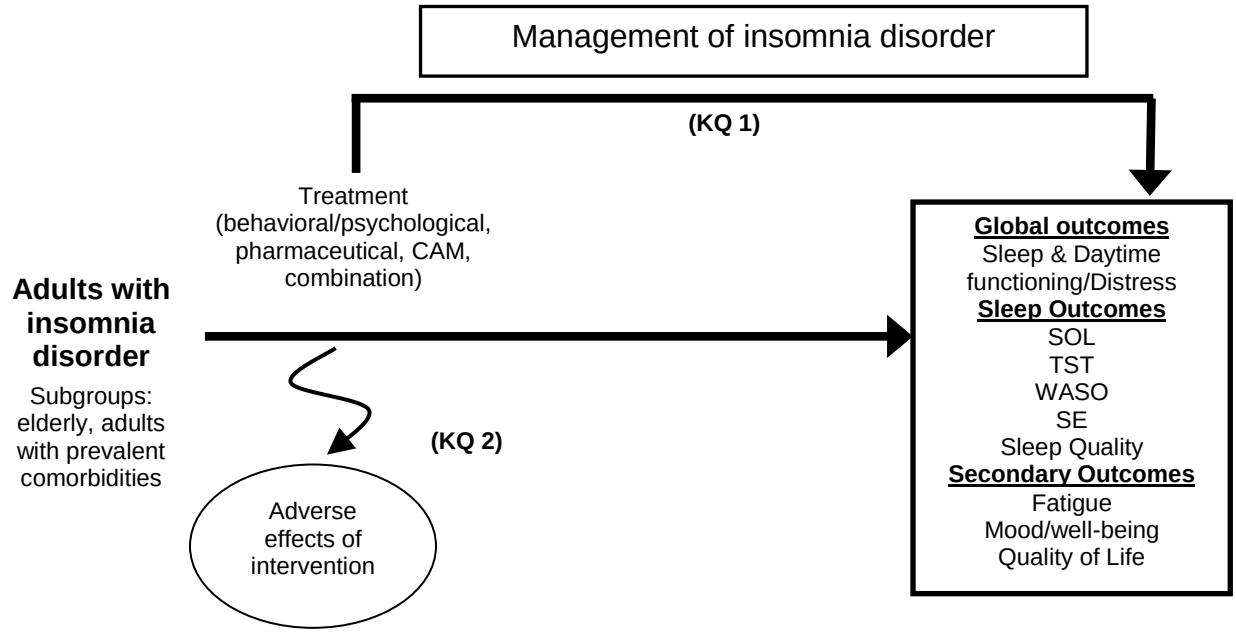
- Any outpatient setting

Methods

Analytic Framework

Figure 1 provides an analytic framework to illustrate the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.

Figure1. Analytic framework



Criteria for Inclusion/Exclusion of Studies in the Review

We included or excluded studies based on the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 3. Treatments for insomnia disorder in primary care settings needed to address certain subpopulations such as the elderly. Coexisting diseases are common among patients with sleep problems, so we include studies that enrolled participants with certain comorbidities. Certain medical or mental health conditions (e.g., pregnancy, menopause, major depressive disorder, bipolar disorder, post-traumatic stress disorder, fibromyalgia, rheumatoid arthritis, Parkinson's disease, etc.) may explain insomnia symptoms, and not meet diagnostic criteria for insomnia disorder. These conditions deserve the attention of a separate review and are considered outside the scope of this review.

Because insomnia disorder is a chronic condition, we felt strongly that a minimum 4-week study duration was appropriate. However, during screening, we noted that a large proportion of drug trials were excluded because they were shorter than 4 weeks, thus limiting the number of drugs that we could evaluate and the number of trials for each included drug. Therefore, we decided to capture and report relevant results from previous fair to high quality systematic reviews (according to AMSTAR criteria) that included trials with any duration. These results, when available, are reported for each drug. These results are not used to replace the *de novo* extraction process and are presented only for comparison purposes. Any large variations from previous systematic review results and our results were investigated.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study enrollment	• Adults with diagnoses consistent with insomnia disorder: o efficacy/comparative effectiveness: 4 weeks to 3 months o sustained efficacy/comparative effectiveness: over 3 months • Exclusive subgroups of adults(older adults, adults with specific comorbid disorders)
Study design and quality	• Systematic reviews and RCTs
Publication type	• Published in peer reviewed journals.
Language of publication	• English

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We searched Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Library to identify previous systematic reviews and randomized controlled trials published and indexed in bibliographic databases from 2004 through November 2013 (Appendix A). We chose our beginning literature search date in 2004 because previous systematic reviews with ending search dates from 2003 to 2005 were available. We identified eligible studies published prior to 2004 through these systematic reviews. Our search strategy included relevant medical subject headings and natural language terms for the concept of insomnia. This concept was combined with filters to select randomized controlled trials (RCTs) and systematic reviews. Bibliographic database searches were supplemented with backward citation searches of highly relevant systematic reviews. We relied on previous systematic reviews to identify studies published prior to 2004. Studies that were rated low or moderate risk of bias and had study durations of 4 weeks or more were identified in the previous Agency for Healthcare Research and Quality (AHRQ) review.[29] This review is not an update of that review, but our Key Questions overlap with the previous AHRQ review. Other reviews were important to identify studies not included in the AHRQ review.[30-33] We will update searches while the draft report is under public/peer review.

Two independent investigators reviewed titles and abstracts of search results to identify systematic reviews and trials evaluating interventions for insomnia. Citations deemed eligible by either investigator underwent full text screening. Two investigators independently screened full text to determine if inclusion criteria were met. Discrepancies in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We documented the inclusion and exclusion status of citations undergoing full-text screening.

We conducted grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and FDA databases. We searched ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for ongoing studies. We also reviewed Scientific Information Packets (SIPs) sent by manufacturers of relevant interventions. Grey literature search results were used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

Data Abstraction and Data Management

We used data from relevant comparisons in previous systematic reviews to replace the *de novo* extraction process when the comparison was sufficiently relevant and the systematic review quality were assessed as fair or high (according to methods described below). Data from RCTs in

included systematic reviews was not extracted separately to avoid double-counting study results, except in cases where additional analyses were required based on our inclusion criteria.

Remaining RCTs meeting inclusion criteria were distributed among investigators for risk of bias assessment and data extraction. For studies assessed as having low to moderate risk of bias (according to methods described below), one investigator extracted relevant study, population demographic, and outcomes data. Data fields extracted included author, year of publication; setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, duration), followup duration, participant baseline demographics, comorbidities; insomnia definition, method of diagnosis and severity, descriptions and results of primary outcomes and adverse effects, and study funding source. Relevant data was extracted into Excel spreadsheets for descriptive analysis. Data was analyzed in RevMan 5.2[34] software. Data used in quantitative synthesis was checked for accuracy by a second investigator. Data appearing in final evidence tables uploaded to the Systematic Review Data Repository will be verified for accuracy by one investigator once it is in the correct format.

Assessment of Methodological Risk of Bias of Individual Studies

Quality of systematic reviews meeting eligibility criteria was assessed using AMSTAR criteria.[35] Two investigators independently assessed risk of bias for included RCTs using questionnaires developed from the Cochrane Risk of Bias tool. The seven domains included in this tool include sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (i.e., was incomplete outcome data adequately addressed), selective reporting, and other sources of bias (i.e., problems not covered by other domains). Additional items were added to assess potential sources of risk-of-bias not addressed by the Cochrane tool. These items were adapted from the AHRQ methods guidance.[36] These items (such as adequacy of intervention definition and implementation) were especially necessary to adequately capture all potential risk of bias associated with psychological interventions. Specific study methodology or conduct was used to judge potential risk of bias with respect to each domain following guidance in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0.[37] Each investigator summarized overall risk of bias for each study classifying it as low, moderate, or high based upon the collective risk of bias inherent in each domain and their confidence that the results are believable given the study's limitations. Both investigators summary Risk of Bias assessments were aggregated. Studies that two investigators rated as high risk of bias were excluded from analysis.

Data Synthesis

When a comparison was adequately addressed by a previous systematic review of acceptable quality and no new studies are available, we reiterated the conclusions drawn from that review. When new trials were available, previous systematic review data was synthesized with data from additional trials by rerunning pooled analysis.

We summarized study characteristics and outcomes of RCTs not included in previous eligible systematic reviews in evidence tables. We grouped studies by population, intervention, and comparison. Studies that included adults of any age were classified as general adult population; studies that included only older adults (age cut-offs varied among studies) were classified as older adults. We assessed the clinical and methodological heterogeneity and

variation in effect size to determine appropriateness of pooling data.[38] Pooling was conducted when populations, interventions, and outcomes were sufficiently similar. Meta-analysis was performed using random effects models (DerSimonian and Laird models using RevMan 5.2[25] software). We calculated risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary primary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs were calculated for continuous outcomes. We assessed statistical heterogeneity with Cochran's Q test and measured magnitude with I^2 statistic.[38] An I^2 score of 50 percent suggests moderate heterogeneity and 75 percent or greater indicates substantial heterogeneity among studies.

We attempted to identify minimum important differences to assess efficacy and comparative effectiveness of instruments measuring global outcomes and sleep outcomes. When MIDs were clearly established, these were used to conclude efficacy or comparative effectiveness. We identified MIDs for several outcome measures (Table 4). The use of minimum important differences offers advantages and disadvantages. The limited literature addressing minimum important difference with respect to these populations and outcomes provides an indication that those we identified are less than "clearly established." Therefore, we reported both statistical differences and statistical differences that exceed minimum important differences. When we did not find an established MID in the literature, we used statistical differences to assess efficacy and comparative effectiveness.

Table 4. Minimum important differences for determining efficacy and comparative effectiveness

Outcome	Measurement/Instrument Properties	MIDs Reported in Literature
Global Outcomes -		
Insomnia Severity Index (ISI)	7 Likert items; range 0-28;[39] Score interpretation: 0-7-no clinically significant insomnia 8-14-subthreshold insomnia 15-21-clinical insomnia (moderate severity) 22-28-clinical insomnia (severe)	Responder - 7 point decrease in score from baseline[40] Remitter - achieve total score below 8 at endpoint[39]
Pittsburgh Sleep Quality Index (PSQI)	7 components; 19 items; range 0-21 with higher scores indicating better sleep[39]	Remitter - total score below 5 at endpoint[41]
Sleep Outcomes		
Sleep-onset latency	Minutes	≤30 minutes at endpoint[41] ↓ 50% from baseline[41]
Wake time after sleep onset	Minutes	≤30 minutes at endpoint[41]
Total sleep time	Minutes	None identified
Sleep efficiency	% (time in bed/total sleep time)	>80 at endpoint[42]
Sleep quality	Subjective assessment using a variety of questions typically rated on a Likert scale.	None identified

Grading the Strength of Evidence for Individual Comparisons and Outcomes

The overall strength of evidence for primary outcomes within each comparison will be evaluated based on five required domains: 1) study limitations (risk of bias); 2) directness (single, direct link between intervention and outcome); 3) consistency (similarity of effect direction and size); 4) precision (degree of certainty around an estimate); and 5) reporting bias.[43] Evidence from previous systematic reviews was reassessed based upon the information provided (evidence quality or attributes of the data and included studies) by the systematic review. Based on study design and conduct, study limitations were rated low, moderate, or high. Consistency

was rated as consistent, inconsistent, or unknown (e.g., single study) after comparing the direction and size of the effect across studies. Directness was rated direct or indirect depending upon whether the outcome measured had a direct link to patient wellbeing and if comparisons were direct. Precision was rated precise or imprecise based upon whether confidence intervals contain or exceed clinical differences. Reporting bias was rated as undetected or suspected after assessing the presence of publication bias, selective outcome reporting bias, and selective analysis bias. Reporting bias was assessed by comparing methods section with results to identify outcomes or analysis not planned or reported. Other factors considered in assessing strength of evidence included dose-response relationship, the presence of confounders, and strength of association. These factors were used to upgrade or downgrade strength of evidence assessments arising from the five required domains. A strong association was suggested when the total number of trials, total number of participants, and effect size demonstrate a robust outcome. Based on these factors, the overall strength of evidence for each outcome was rated as:[43]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Assessing Applicability

Applicability of studies was determined according to the PICOTS framework. Study characteristics affecting applicability include, but are not limited to, the population from which the study participants are enrolled (i.e., studies enrolling participants from sleep medicine clinics may not produce results applicable to the general population of patients being treated for insomnia in primary care clinics), narrow eligibility criteria, and patient and intervention characteristics different from those described by population studies of insomnia.[44] Specific factors that could modify the effect of treatment and affect applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics such as age.

Results

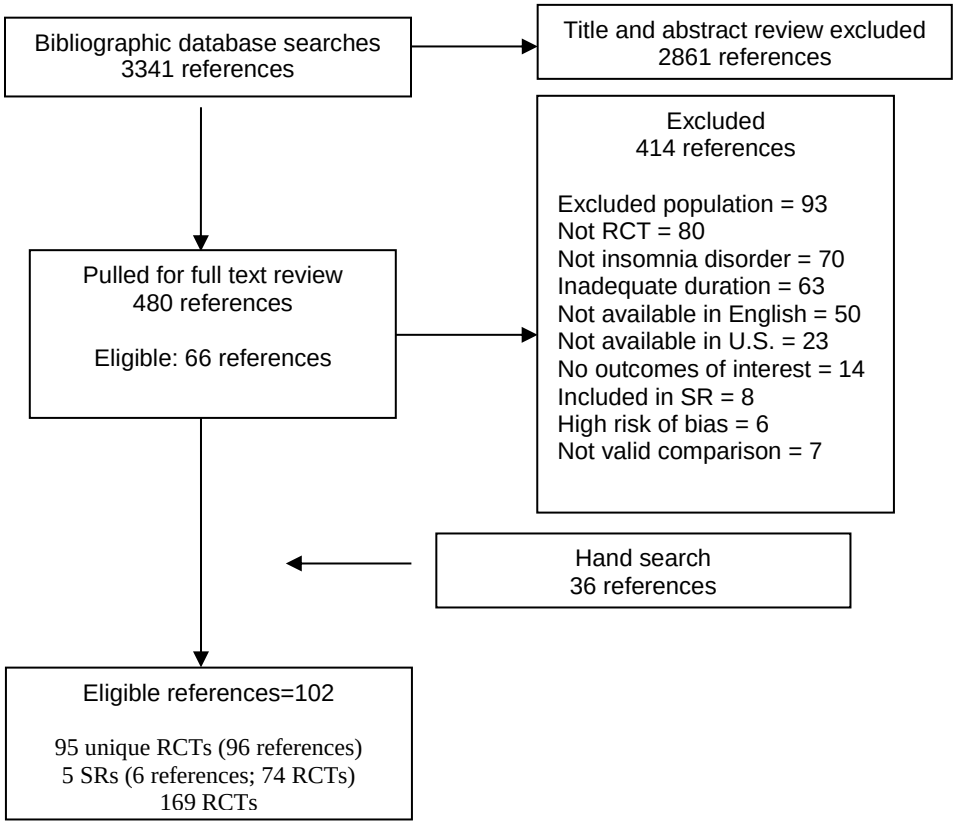
Literature Search and Screening

Key Points

- Global outcomes were less often measured than sleep outcomes, especially in the drug studies; recent research was more likely to assess global outcomes.
- Minimum important differences were identified for some instruments used to assess global outcomes, but these were not frequently used nor is it clear whether they are well established. We did not identify established minimum important differences for most sleep outcomes. Remission defined using sleep onset latency and sleep efficiency were the exceptions.
- A large body of literature tests a wide variety of treatments for insomnia disorder. Strength of evidence suffers because of limited studies with similar comparisons. In addition, sample sizes were typically small and studies often contained multiple arms. Older studies often did not provide data sufficient for analysis.

Our search identified 3341 citations, of which 480 required full text review after title and abstract screening (Figure 2). We completed a full-text review of 480 references and hand searched key systematic reviews to identify 102 eligible references representing 100 unique studies. Studies excluded after full text review are listed in Appendix B along with exclusion reasons. The most frequent exclusion reasons included a lack of randomization, inadequate study duration, drugs not approved for use in the United States, insomnia not clinically diagnosed, and not available in English. Studies not available in English were often complementary and alternative medicine (CAM) treatments published only in Chinese. We captured results of many of these studies by including systematic reviews (that did not have language restrictions) in lieu of de novo extraction. The literature included in our analysis consists of 95 unique randomized controlled trials (RCTs) and 5 unique systematic reviews that synthesize evidence from 74 unique RCTs for a total of 169 RCTs.

Figure 2. Literature flow diagram



Evidence tables including study characteristics and outcomes for all included studies are available upon request and will be uploaded to the Systematic Review Data Repository after the final version of this report is posted. AMSTAR ratings, risk of bias assessments, and strength of evidence assessments appear in Appendix C for psychological interventions; Appendix D for pharmacologic interventions; Appendix E for CAM interventions; and Appendix F for combination or comparative effectiveness of interventions across intervention types.

Efficacy and Comparative Effectiveness of Psychological Interventions

Efficacy of Cognitive Behavioral Therapy in the General Adult Population

Key Points

- The efficacy of CBT-I across several delivery modes in the general adult population is well studied; low to moderate strength evidence shows that it improves global outcomes by minimum important differences; moderate strength evidence shows that global outcomes are statistically significantly better with CBT-I than passive control; low to moderate-strength evidence shows that sleep outcomes are improved; however, improvements in sleep outcomes are relatively modest.

- Evidence of CBT-I's efficacy in older adults was insufficient to assess minimum important differences in global outcomes; evidence was insufficient to assess sleep onset latency and total sleep time; moderate-strength evidence shows that CBT decreases wake time after sleep onset by nearly 50 minutes and improves sleep efficiency by 12 points. Low-strength evidence shows that sleep efficiency improved by over 12 percentage points.
- Evidence on the efficacy of multicomponent behavioral treatment in the general adult population was limited. Low strength evidence shows that sleep onset latency improved; evidence for all other outcomes and adverse effects were insufficient.
- Evidence on the efficacy of multicomponent behavioral treatment or BBT in older adults was more robust; low strength evidence shows that global outcomes were improved statistically; moderate strength evidence showed that sleep onset latency, wake time after sleep onset, and sleep efficiency were improved with multicomponent behavioral treatment or BBT; improvements in sleep outcomes were modest.
- Evidence on the efficacy specific behavioral interventions alone (stimulus control, sleep restriction, relaxation techniques) was limited; sufficient evidence was available for few outcomes:
    - Moderate-strength evidence shows that sleep restriction decreased wake time after sleep onset in older adults; low-strength evidence showed no statistically significant improvement in total sleep time; evidence for all other outcomes was insufficient.
    - Low-strength evidence shows that stimulus control improves total sleep time in the general adult population and older adults. Low strength evidence shows that wake time after sleep onset with no different from passive control in the general adult population. Evidence for all other outcomes was insufficient.
    - Low-strength evidence shows that relaxation techniques decrease sleep onset latency in the general adult population; evidence for all other outcomes was insufficient.
    - Evidence comparing different psychological interventions was insufficient to conclude that any one treatment is more efficacious than another.

Overview of Studies

We included studies as efficacy of CBT-I if they had an active CBT-I arm and passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We identified 17 RCTs that assessed the efficacy of CBT-I to treat insomnia disorder in the general adult population.[40,45-60] Most studies were conducted in the United States. Studies differed in delivery method of CBT-I. Five studied individual in-person CBT-I,[47,48,53,55,56] three studied group CBT-I,[49,51,52] one studied phone-delivered CBT-I,[45] four studied Web-based CBT-I,[50,57,58,60] three studied book-based CBT-I,[40,46,54] and one studied a multimedia CBT-I.[59] The mean age was typically in the mid-40s; participants were predominantly women, and most were white (in the trials that reported race). Risk of bias of included trials was predominantly low to medium. Data were pooled when studies provided the same outcomes and sufficient data to pool (Table 5).

Table 5. Overview and strength of evidence: efficacy of CBT-I in the general adult population

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95%CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs.					

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95%CI]; I^2	Strength of Evidence (Rationale)
passive control *(17 RCTs; N=1878)*					
Global Outcomes					
Remission	4 (115)	56% (64/60)	18% (10/55)	Favors CBT RR= 2.52 [1.50 to 4.22] ARR= 38% NNT= 3	Moderate (moderate study limitations)
Responder (ISI score change of 7[53] or 8[45] points)	2 (62)	66% (21/32)	17% (5/30)	Favors CBT RR= 4.56 [0.54 to 38.50] ARR= 49% NNT=2.0	Low (moderate study limitations, imprecise)
ISI score	4 (200)			Favors CBT WMD= -4.63 [-6.42 to -2.85]	Moderate (moderate study limitations)
PSQI score	4 (307)			Favors CBT WMD= -2.86 [-3.69 to -2.02]	Moderate (moderate study limitations)
CGI="very much improved"	1 (60)	35% (13/37)	4% (1/23)	Favors CBT RR= 8.08 [1.13 to 57.73] ARR= 31% NNT=2.0	Insufficient (moderate study limitations, imprecise, unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	11 (1049)	-	-	Favors CBT-I WMD= -11.34 [-18.00 to -4.68]	Moderate (moderate study limitations)
Total sleep time, self-report, minutes	13 1091)	-	-	Favors CBT-I WMD= 11.24 [1.45 to -21.03]	Moderate (moderate risk study limitations)
Wake time after sleep onset, self-report, minutes	9 (734)	-	-	Favors CBT-I WMD= -26.41 [-40.97 to -11.84]	Moderate (moderate study limitations)
Sleep efficiency	12 (1059)			Favors CBT-I WMD= 6.13 [3.23 to 9.03]	Moderate (moderate risk study limitations)
Sleep quality	10 (840)	-	-	Favors CBT-I SMD= 0.43 [0.20 to 0.67]	Moderate (moderate study limitations)

ARR=absolute risk reduction; CI=confidence intervals; ND=No statistically significant difference; NNH=number needed to harm; NN =number needed to treat; RR=risk ratio; =weighted mean difference

Global Outcomes

Four studies assessed insomnia remitters (achieving an ISI score ≤7 or PSQI score ≤5 at followup) (Figure 3).[45,47,48,53] Two small studies used the "ISI score ≤7" definition of remission. Jansson-Fröjmark et al. compared individual CBT-I to waitlist controls[53] and Arnedt et al. compared CBT-I delivered by phone with a control group who received sleep hygiene information.[45] Both studies had small sample sizes and failed to reach statistical significance. Pooled results show that the CBT-I participants were twice as likely to achieve remission from insomnia. Two studies used the "PSQI score ≤5" definition of remission. Edinger et al. 2003 and Edinger et al. 2009 compared individual CBT-I with sleep hygiene education.[47,48] The smaller study did not reach statistical significance,[47] but the larger one did.[48] Pooled results show that CBT-I participants are three times as likely to achieve remission. Pooled results for the four studies demonstrate that CBT-I participants are more than twice as likely to achieve remission; 38 percent more CBT-I participants achieved remission compared with passive controls; and 3 individuals with insomnia would need to be treated to see one achieve remission.

Jansson-Fröjmark et al. and Arnedt et al. defined "responder" differently using the ISI as a 7 or 8 point reduction in ISI score indicating response to treatment, respectively (Figure 4).[45,53] Both studies demonstrate greater response in the CBT-I groups, but the response rates differed greatly (RR = 16.89 vs. 2.40). The more stringent, 8-point response definition could partially explain the lower response rate with CBT-I delivered by phone[45] or the impact of CBT-I by phone may be lower than that of in-person CBT-I.[53] Despite statistically significant effects at the study level, the pooled result was not statistically significant.

Four of the CBT-I efficacy studies across four delivery methods reported mean ISI scores (Figure 5).[45,53,56,60] Only individual CBT-I achieved a weighted mean change in ISI scores equal or greater than the minimum important difference of seven with a pooled weighted mean difference of 6.9.[53] Three of the four studies showed statistically significant improvements in ISI scores. The pooled estimate shows that CBT-I across delivery methods achieves a nearly 5-point reduction in ISI scores. CBT-I delivered by phone[45] showed the smallest mean change (-3.1) and Web-based CBT-I resulted in only a slightly higher mean change (-3.8) in ISI scores.[60] Four studies across four delivery methods reported mean PSQI scores (Figure 6).[45,48,51,54] The pooled estimate showed that CBT-I across delivery methods achieved nearly a 3-point reduction in PSQI scores. We did not identify literature suggesting a minimum important difference, so it is unclear how this change should be interpreted.

One last global outcome was evaluated in CBT-I efficacy trials, CGI. Vincent, et al., showed that clinicians of participants enrolled in web-based CBT-I were eight times more likely to report "much or very much improved" compared to passive controls.[60]

Figure 3. Efficacy of CBT-I in the general adult population: remitters

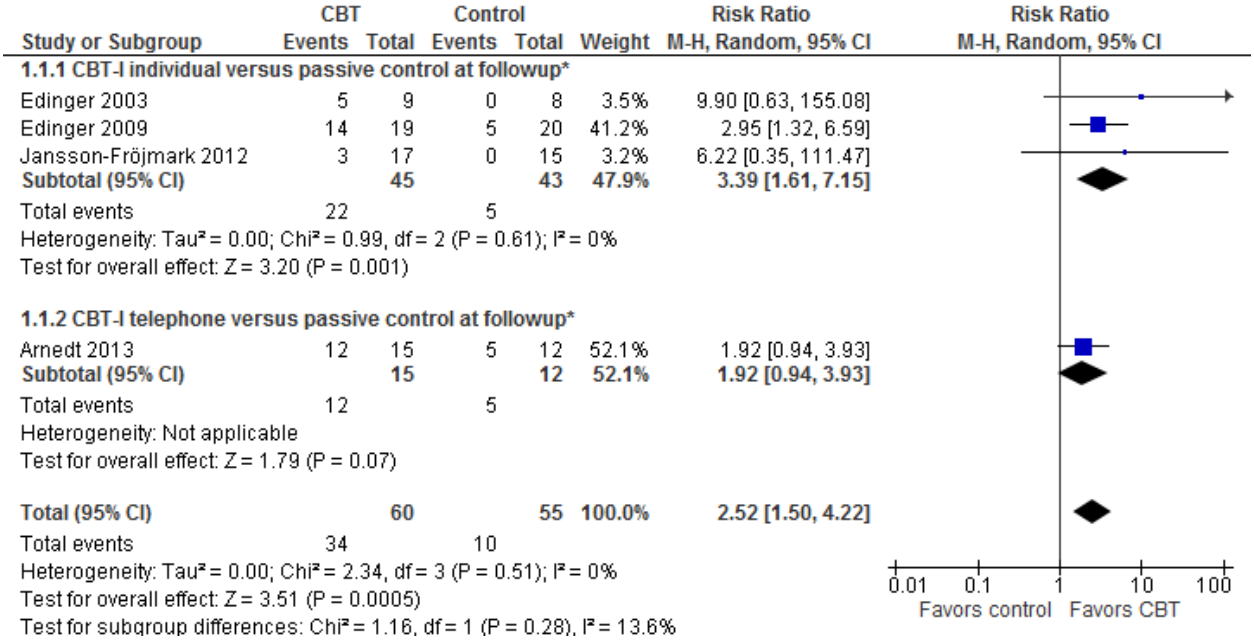
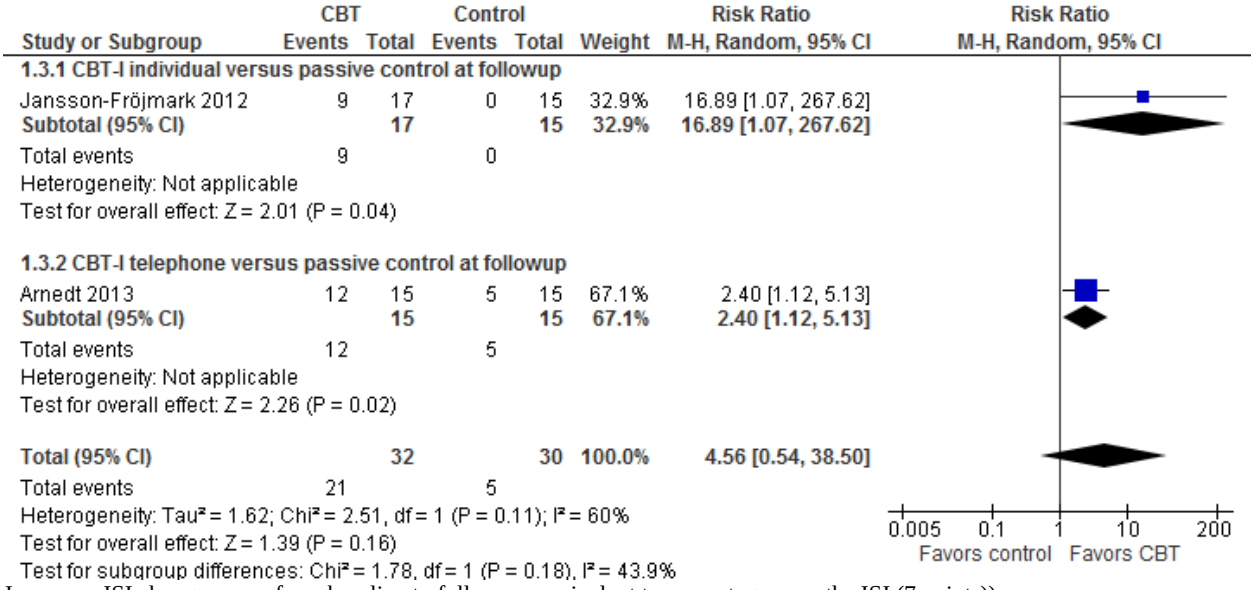


Figure 4. Efficacy of CBT-I in the general adult population: responders



Jansson = ISI change score, from baseline to followup, equivalent to one category on the ISI (7 points))
Arnedt = a post-treatment score >8 points less than the pretreatment score

Figure 5. Efficacy of CBT-I in the general adult population: ISI mean score

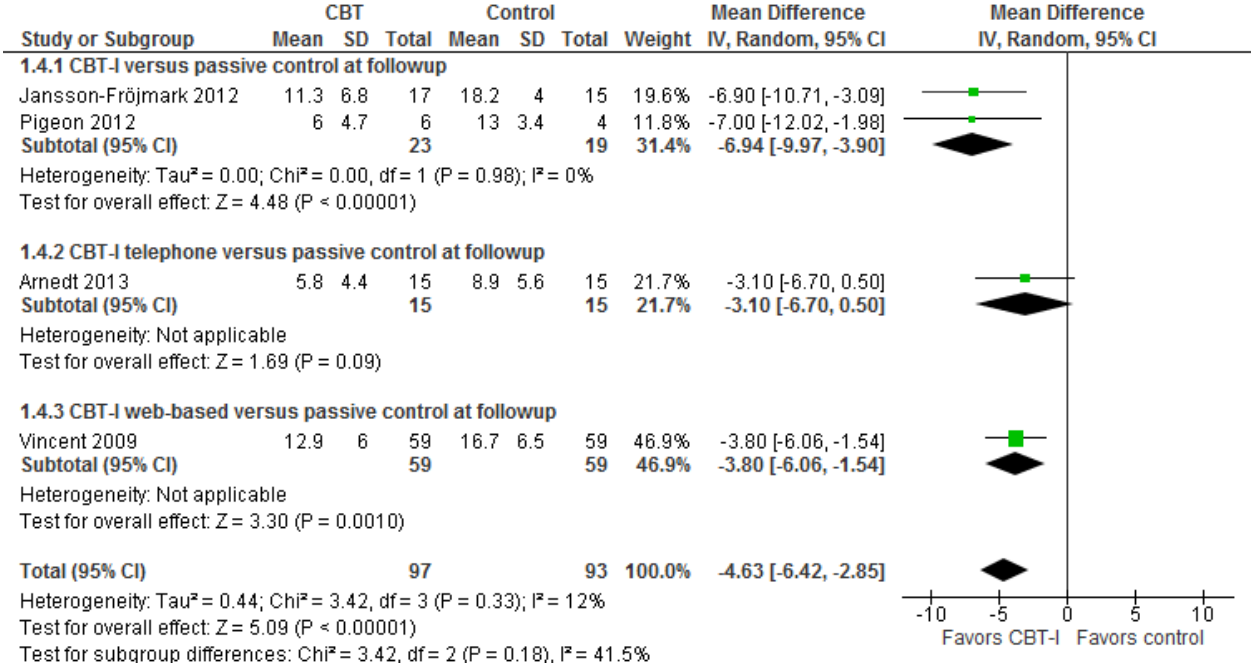
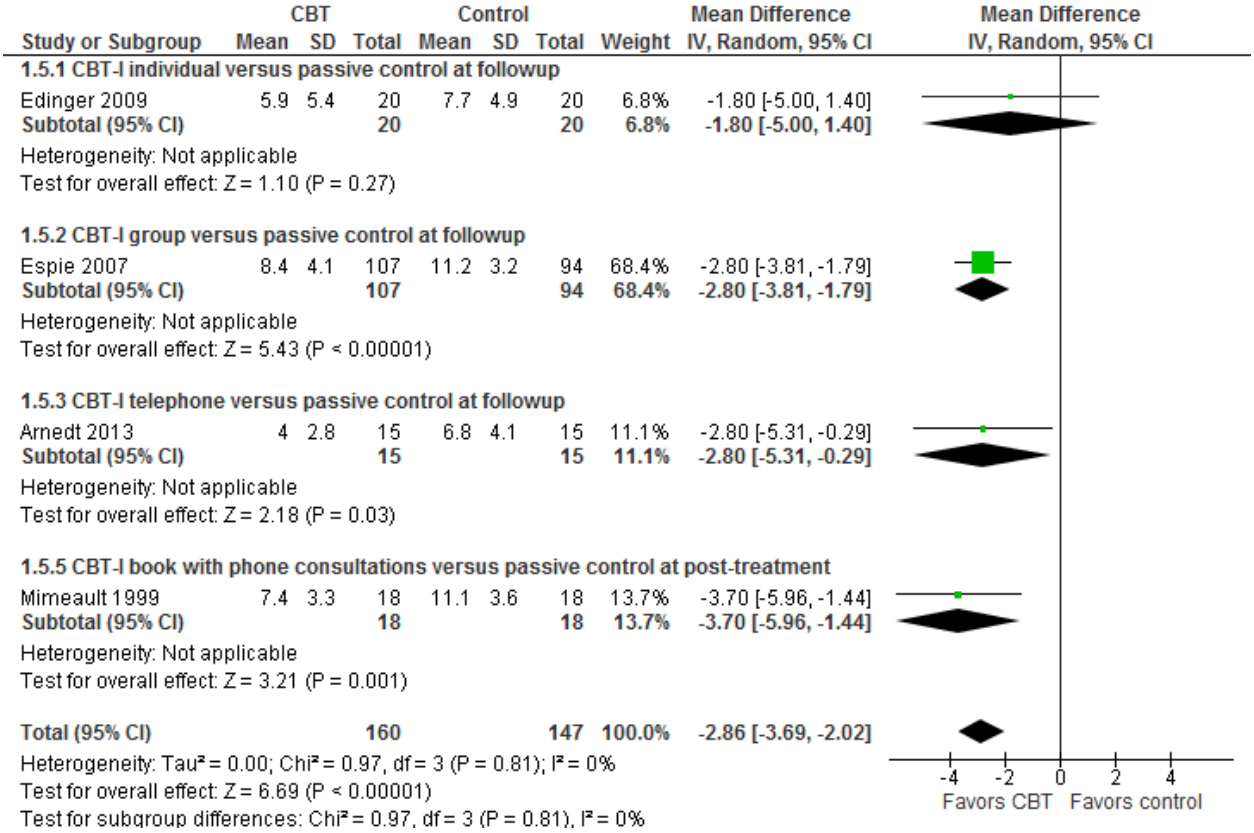


Figure 6. Efficacy of CBT-I in the general adult population: PSQI scores



Sleep Outcomes

All CBT-I efficacy trials reported sleep outcomes (Figures 7-9). Improvements in sleep onset latency differed significantly from passive control in only four of the 10 trials that reported poolable data (Figure 7). Pooled data show that the largest improvements in sleep onset latency occurred with Web-based CBT-I. However, this was due to a very large effect in one trial with a relatively large sample size and a reported mean decrease in sleep onset latency of more than 41 minutes.[50] The pooled estimate across all delivery methods shows that CBT-I participants reduced their sleep onset latency by more than 11 minutes compared to passive controls.

Total sleep time increased with statistical significance compared with passive treatment controls across 13 trials (Figure 8).[50] CBT-I participants gained a mean of 11 minutes of sleep.

Reductions in wake time after sleep onset were demonstrated in five of nine trials reporting this outcome across four delivery methods. Again, the Espie et al. trial showed the largest gains. The pooled estimate shows that CBT-I participants decreased their mean time awake time after sleep onset by more than 26 minutes.

Post-intervention sleep efficiency improved with CBT-I in six of 12 trials. Mean sleep efficiency at endpoint ranged from 71.7 to 91.5 among CBT-I participants and from 64.9 to 85.6 among passive controls across the nine trials. The pooled estimate shows that sleep efficiency improved by 6 percentage points in CBT-I participants compared with passive controls across six delivery methods.

Sleep quality improved in five of 10 trials reporting sleep quality (Figure 11). CBT-I delivered in person one on one or in groups demonstrated consistent improvements. CBT-I delivered one on one was the only method that achieved a large response. The pooled estimate of the standardized mean difference suggests that CBT-I creates a moderately sized improvement on sleep quality across delivery methods.

Figure 7. Efficacy of CBT-I in the general adult population: sleep onset latency at followup

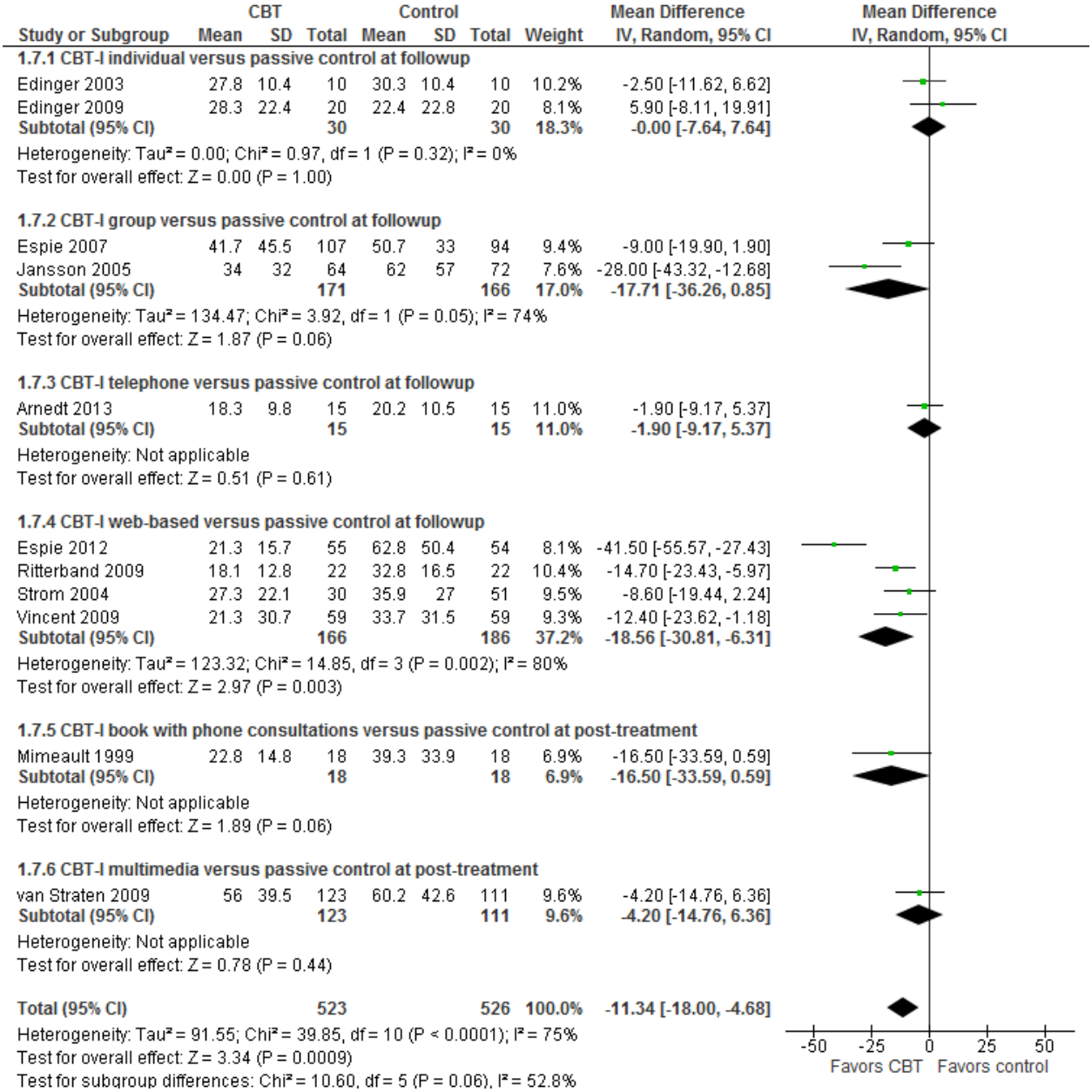


Figure 8. Efficacy of CBT-I in the general adult population: total sleep time

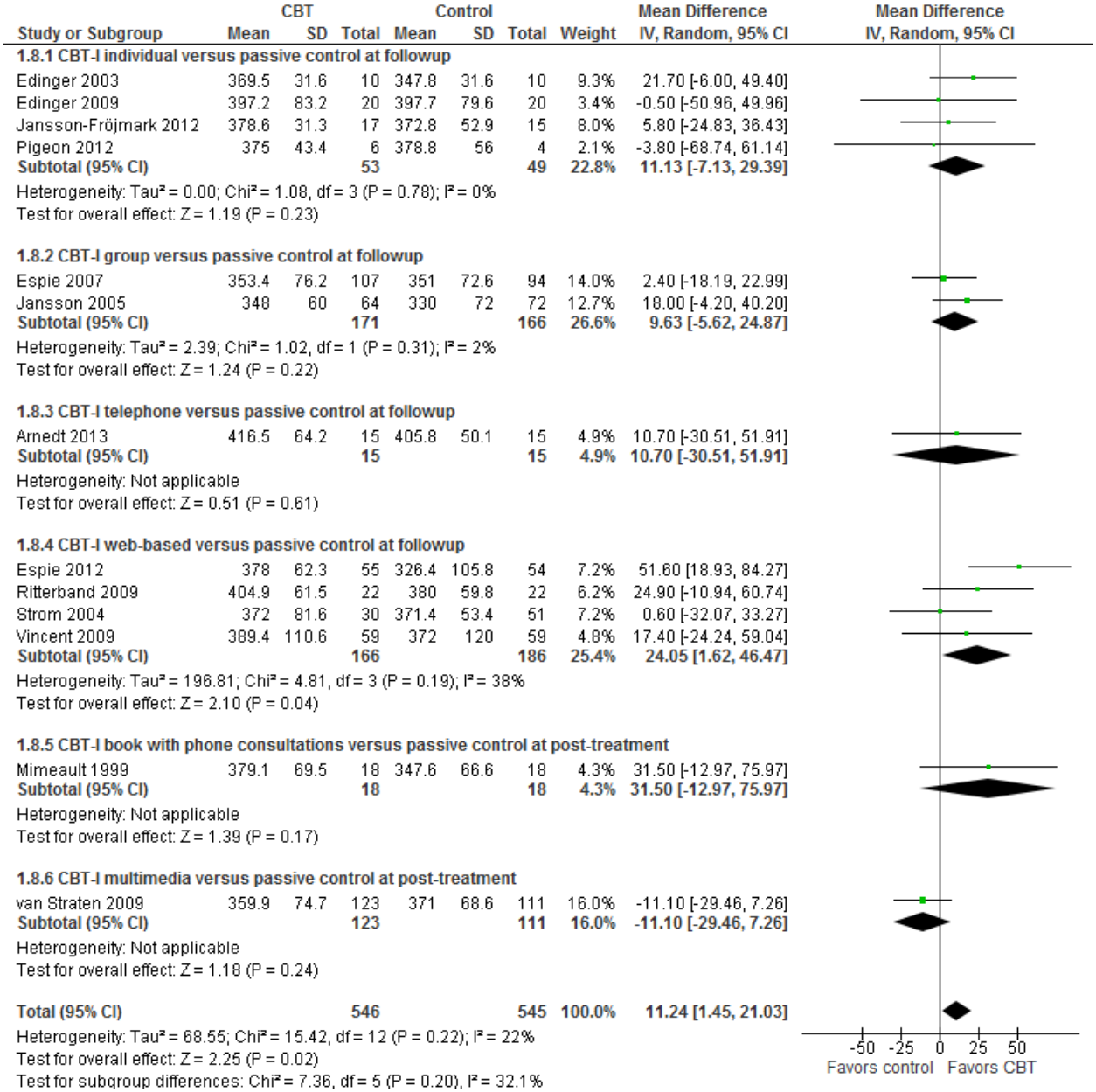
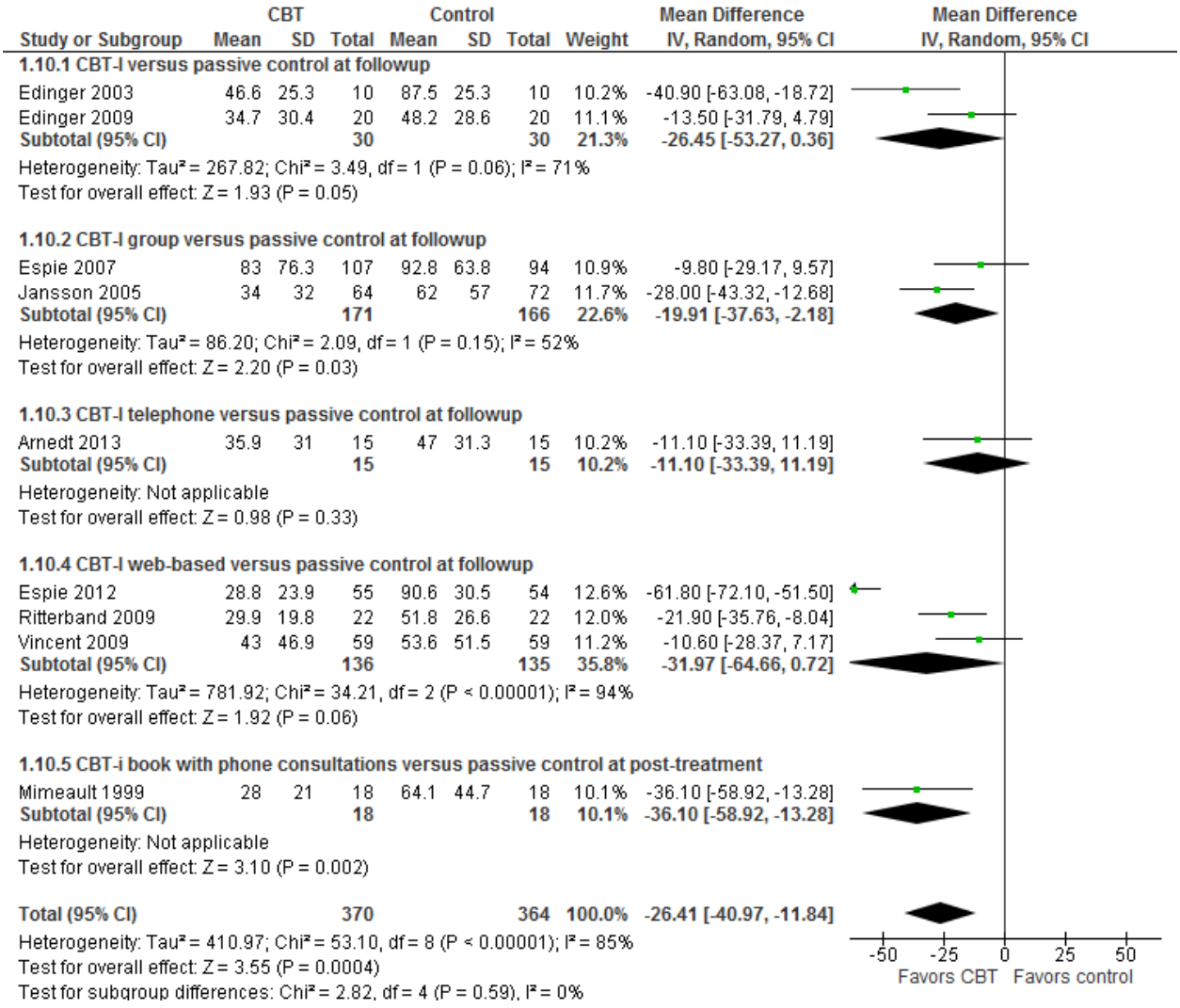


Figure 9. Efficacy of CBT-I in the general adult population: wake time after sleep onset



Secondary Outcomes

Several studies reported secondary outcomes. Several trials mentioned secondary outcomes using several different instruments. Most studies were small and few studies used similar instruments.

Adverse Effects

Specific adverse effects were not reported. Thirteen trials reported withdrawals or loss to followup. Two studies did not report withdrawals or loss to followup by treatment group.[49,52] No statistically significant differences were found across groups in the rates of withdrawals or loss to followup.

Efficacy of Cognitive Behavioral Therapy in Older Adults

Overview of Studies

We included studies as efficacy of CBT if they had an active CBT-I arm and a passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We analyzed studies that enrolled older adults separately from those enrolling adults of all ages. We identified four trials that compared CBT-I to a passive control in older adults.[61-64] Risk of bias for included studies was predominantly moderate. We pooled evidence on common outcomes when possible (Table 6). Two other trials specifically enrolled older adults with pain.[65,66]

Table 6. Overview and strength of evidence: efficacy of CBT-I in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control *(4 RCTs; N=215)*					
Global Outcomes					
PSQI score	1 (25)			Favors CBT MD= -2.80 [-5.28 to -0.41]	Insufficient (moderate study limitations, imprecise, unknown consistency)
PSQI mean change	1 (129)			Favors CBT MD= 2.20 [1.40 to 3.36]	Insufficient (moderate study limitations, unknown consistency)
ISI mean change	1 (125)			Favors CBT MD= 2.10 [0.55 to 3.65]	Insufficient (moderate study limitations, unknown consistency))
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (48)	-	-	NS	Insufficient (moderate risk of bias, imprecise)
Total sleep time, self-report, minutes	3 (77)	-	-	NS	Insufficient (moderate risk of bias, imprecise)
Wake time after sleep onset, self-report, minutes	3 (77)	-	-	Favors CBT-I WMD= -48.34 [-78.88 to -17.80]	Moderate (moderate risk of bias)
Sleep efficiency	3 (77)			Favors CBT-I WMD= 12.44 [7.62 to 17.26]	Low (moderate risk of bias. Larger effect size)
Sleep efficiency, mean change	1 (123)			Favors CBT-I MD= 11.20 [6.25 to 16.15]	Insufficient (moderate study limitations, unknown consistency)
Adverse Effects					
Withdrawals	2 (126)	13% (4/62)	11% (5/64)	NS	Insufficient (moderate study limitations, imprecise)

CI=confidence intervals; ARR=absolute risk reduction; ND=No statistically significant difference; NNT=number needed to treat; NNH=number needed to harm; RR=risk ratio; WMD=weighted mean difference

Global Outcomes

Two studies reported global outcomes (Figure 10).[61,64] Both reported PSQI, but Rybarczyk et al. reported total scores and Morgan et al. reported mean changes in scores, so data could not be pooled. Rybarczyk et al. did not find significant differences, but the study was small and underpowered (n=25). Morgan et al. found statistically significant difference between the mean change on the ISI and the mean change on the PSQI at three time points. Global outcomes are improved after CBT-I in older adults and improvements are sustained at 3 and 6 month followup.

However mean difference in change between groups or mean change from baseline for the ISI do not achieve the minimum clinical difference of seven points. Similar improvements were demonstrated with the PSQI, however clinical significance of the difference in mean change is unclear (Figure 11).

Figure 10. Efficacy of CBT-I in older adults: ISI

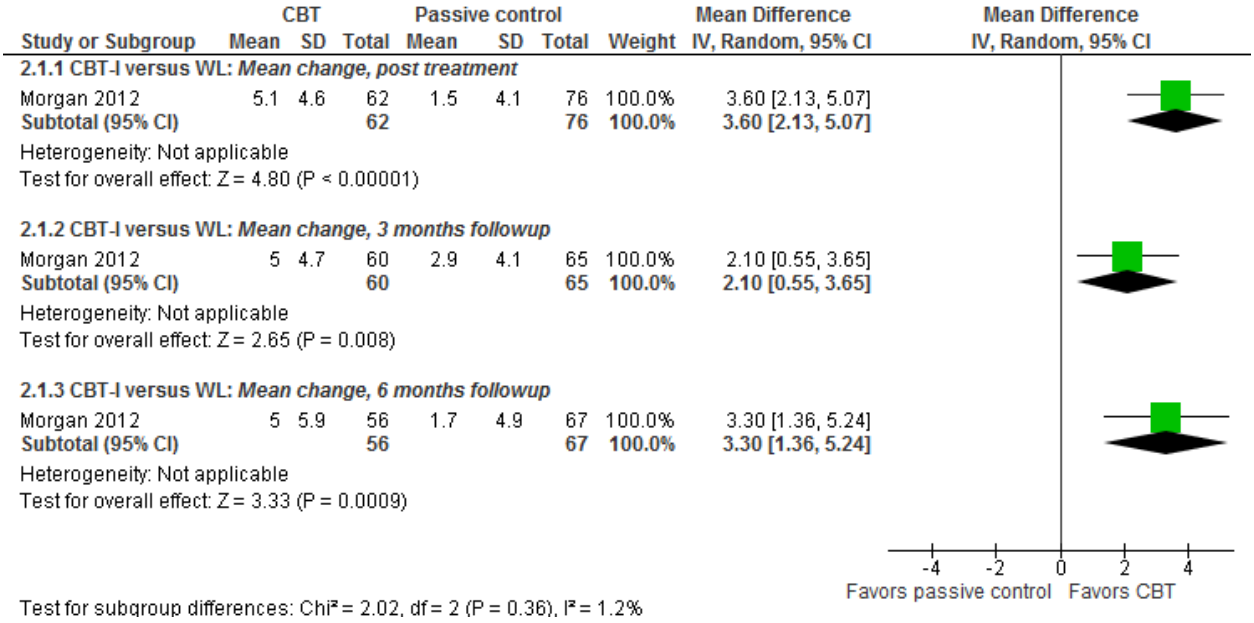
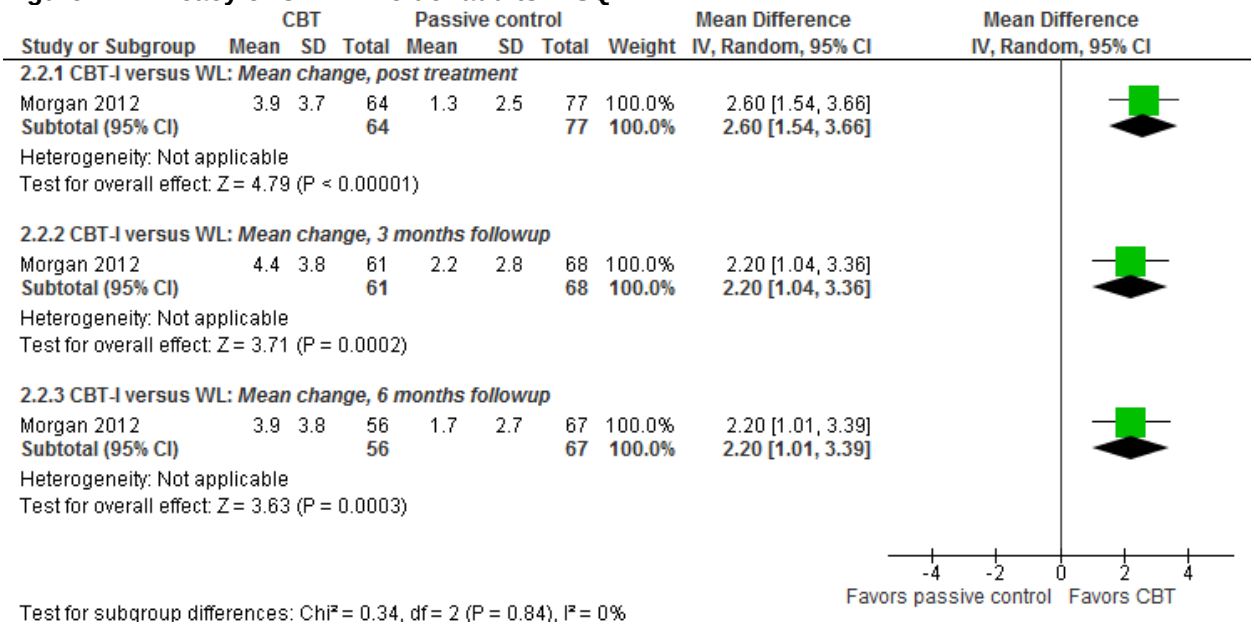


Figure 11. Efficacy of CBT-I in older adults: PSQI



Sleep Outcomes

Sleep outcomes were reported in all CBT-I efficacy trials among older adult participants (Figures 12 and 13). One trial attempted to measure the proportion of participants who achieved clinically significant improvement in sleep.[64] It defined clinically significant improvement as the

attainment of sleep efficacy equal to or greater than the mean in a group of patients without insomnia. More of CBT-I participants achieved clinical improvement than passive controls

Sleep onset latency was reported in two small trials.[63,64] Differences between groups were not significant in either trial or in pooled analysis. No differences were reported in any of the three trials reporting total sleep time at followup.[62-64,67] Pooled analysis was also insignificant post-treatment and at 1- and 2-year followup. Results for two other sleep outcomes were more promising. Wake time after sleep onset was reported in two studies.[63,64] Statistically significant reductions were shown in each individual study as well as with the pooled result. CBT-I participants reduced their wake time after sleep onset by nearly 50 minutes. One study showed that this result was maintained at 1-year but not 2-year followup (however, power to detect a difference was lower for this time point).[62] A similar pattern was demonstrated with sleep efficiency. The pooled analysis demonstrates that the CBT-I group increased their sleep efficiency by nearly 13 percentage points at followup. In Morin et al. sleep efficiency increased to 18 minutes at 1-year followup, but no statistically significant difference was demonstrated at 2-year followup.[62] There was a high attrition rate by the 2-year followup outcomes and the study was underpowered to detect small differences between groups.

Figure 12. Efficacy of CBT-I in older adults: sleep onset latency

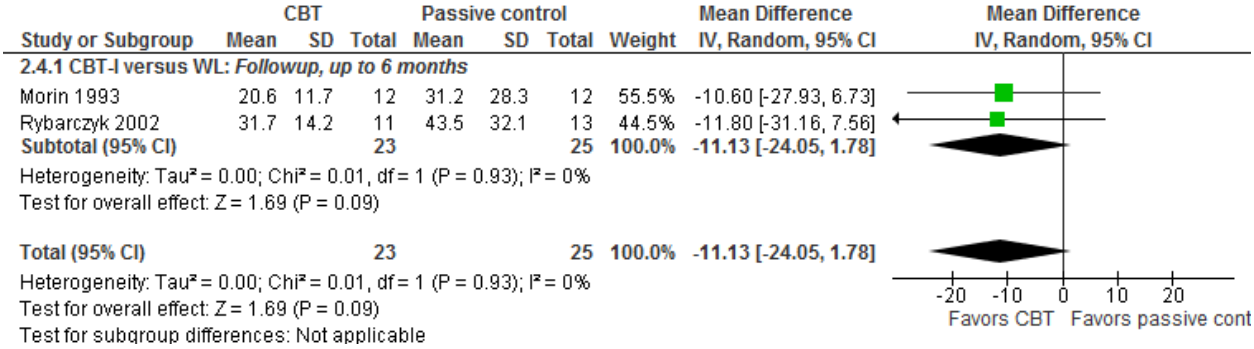
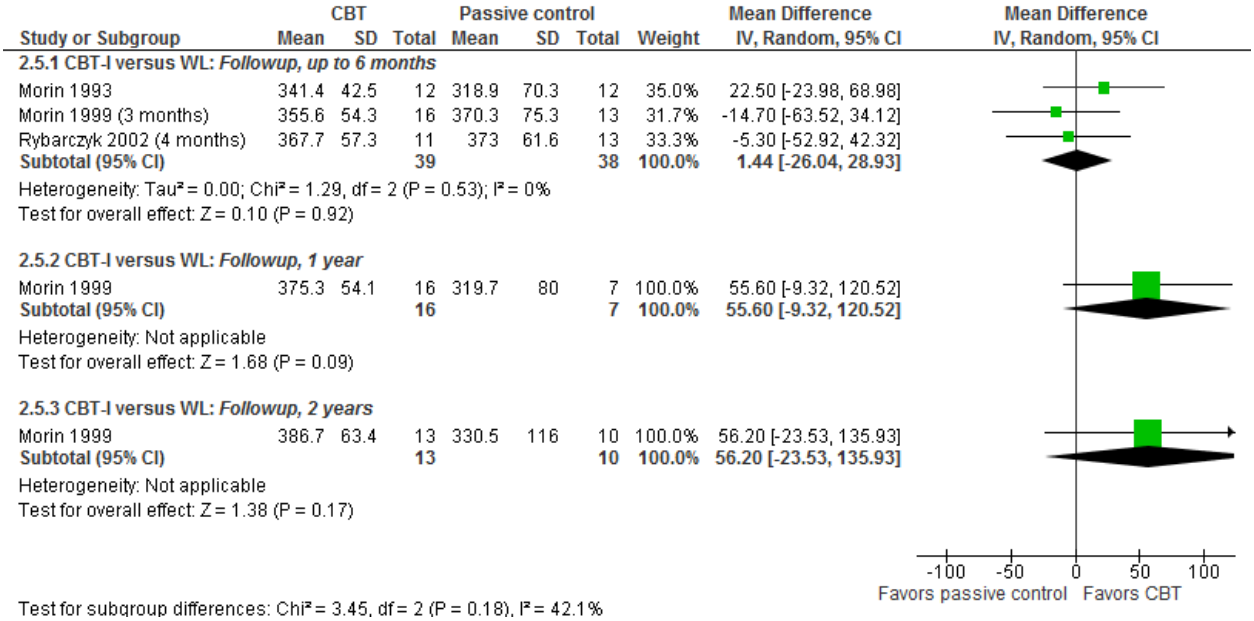


Figure 13. Efficacy of CBT-I in older adults: total sleep time



Secondary Outcomes

Morgan et al. reported Fatigue Severity Scores for both groups and found no statistically significant differences post-treatment, or at 3- or 6-month followup.[61]

Adverse Effects

Three of the four trials reported on withdrawals or adverse effects.[61,64,66] CBT-I participants were no more likely to withdraw from a study than participants of passive control groups. One withdrawal from the CBT-I group was a death, but the death was not associated with treatment.[64]

Additional CBT-I Studies

We identified two studies that compared different types of psychologic interventions. Two studies assessed CBT delivered to patients with pain and insomnia.[65,66] Vitiello et al. (2009) randomized 24 participants with osteoarthritis pain to CBT-I or attention control. Vitiello et al. (2013) randomized 367 participants with pain conditions and insomnia to three treatment groups (CBT-I, CBT-PI (pain and insomnia), or education only). Both CBT groups experienced better outcomes (insomnia severity) than the education group. These studies suggest that the evidence for CBT-I is also applicable to individuals with pain.

Efficacy of Multicomponent Behavioral Interventions or Brief Behavioral Therapy in the General Adult Population

Overview of Studies

We evaluated two randomized trials comparing multicomponent behavioral therapy with passive controls.[68,69] The two trials randomized 203 participants, the mean age was 44, and 68 percent were women (based on one trail reporting sex). Participants had a mean insomnia duration of 14.2 years. One trial was conducted in the United States[68,69] and one in Australia.[68] Woolfolk et al. randomized participants to one of five arms: imagery training, imagery training with muscle tension-release, somatic focusing, progressive relaxation, or waitlist control. Morawetz et al. randomized participants to multicomponent behavioral interventions via a self-help tape, a comparable therapist-led treatment, or waitlist control.[68] Risk of bias was predominantly moderate.

Table 7. Overview and strength of evidence: efficacy of multicomponent behavioral interventions or brief behavioral treatments

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Multicomponent behavioral treatment versus Waitlist *(2 RCTs; N=50)*					
Global Outcomes					
NR		-	-		
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (50)	-	-	Favors BBT WMD=-23.38 [-36.29 to -9.85]	Low (moderate study limitations)
Total sleep time, self-report, hours	1 (9)	-	-	Favors BBT MD=1.10 [0.38 to 1.82]	Insufficient (moderate study limitations, imprecise, unknown consistency)

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Wake time after sleep onset, self-report, minutes	1 (19)	-	-	Favors BBT MD=-29.00 [-53.74 to -4.26]	Insufficient (moderate study limitations, unknown consistency)

BBT=brief behavioral therapy; CI=confidence intervals; MD=mean difference; NR=not reported; WMD=weighted mean difference

Global Outcomes

Neither trial reported global outcomes.

Sleep Outcomes

Sleep outcomes were reported in both multicomponent behavioral interventions efficacy trials. Improvements in sleep onset latency were significantly different than passive control in one of the two (Figure 14).[68] This study reported results in two treatment delivery methods, therapist-led treatment (MD = -21.63 [-42.87 to -0.39]) and self-help tape), both statistically improved sleep onset latency compared with passive control. The pooled estimate shows that BBT participants reduced their sleep latency by more than 23 minutes over passive control participants.

The one trial that reported total sleep time shows a statistically significant increase over passive control patients.[68]

Reduction in wake time after sleep onset was demonstrated in one trial, showing a decrease of 29 minutes.[68]

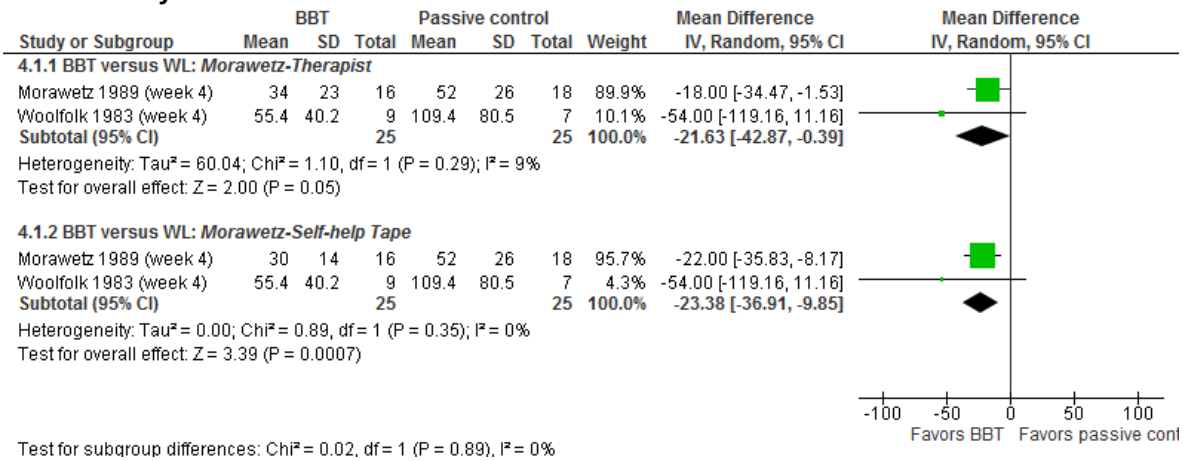
Secondary Outcomes

Neither of the BBT trials reported secondary outcomes.

Adverse Effects

Specific adverse effects were not reported. Both trials reported study withdrawals or loss to followup (15 percent) but neither reported withdrawals or loss to followup by group.

Figure 14. Efficacy of multicomponent behavioral therapy in the general adult population: sleep onset latency



Efficacy of Multicomponent Behavioral Interventions or Brief Behavioral Therapy in Older Adults

Overview of Studies

We evaluated four randomized trials comparing multicomponent behavioral therapies or BBT with passive control in older adults.[70-73] The four trials randomized 181 participants, the mean age was 70, and 67 percent were women. In the two trials reporting, participants had a mean insomnia duration of 15.3 years. Three trials were conducted in the United States.[70-73] Three trials randomized participants to either BBT or information control (such as sleep hygiene).[70-72] In the fourth trial, hypnotic-dependent adults with insomnia were randomized to either BBT or placebo.[73] We synthesized outcomes from these studies when possible (Table 8).

Table 8. Efficacy of multicomponent behavioral therapy or brief behavioral therapy in older adults

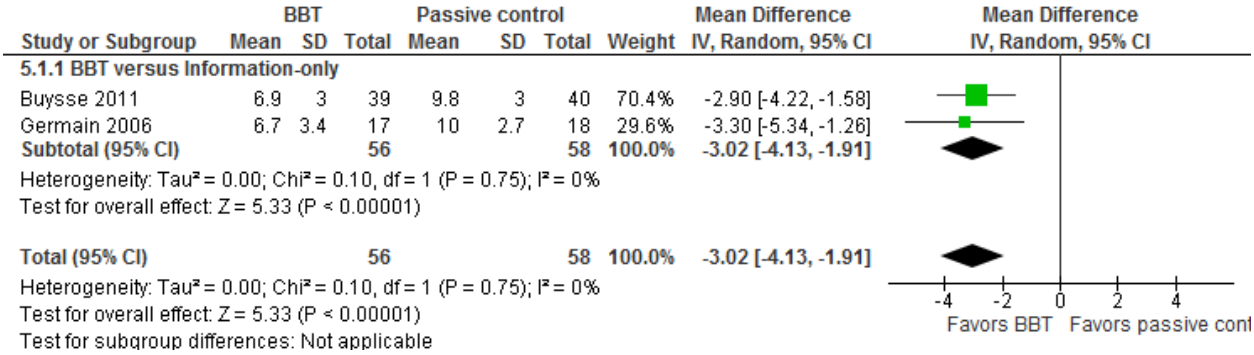
Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
BBT vs. passive control ***(4 RCTs; N=181)***					
Global Outcomes					
PSQI score	2 (114)			Favors BBT WMD = -3.02 [-4.13 to -1.91]	Low (moderate study limitations)
Patients no longer meeting diagnostic criteria for insomnia	1 (78)			Favors BBT MD = 4.20 [1.76 to 10.02]	Insufficient (study limitations, unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	4 (181)	-	-	Favors BBT WMD= -10.36 [-15.57 to -5.15]	Moderate (moderate study limitations)
Total sleep time, self-report, minutes	4 (181)	-	-	NS	Low (moderate study limitations, imprecise)
Wake time after sleep onset, self-report, minutes	4 (181)	-	-	Favors BBT WMD = -13.91 [-21.11 to -6.71]	Moderate (moderate study limitations)
Sleep efficiency	4 (181)	-	-	Favors BBT WMD = 5.11 [2.47 to 7.75]	Moderate (moderate study limitations)

BBT=brief behavioral therapy; CI=confidence intervals; NS=no significant difference; WMD=weighted mean difference

Global Outcomes

In the two trials reporting PSQI scores, participants receiving BBT saw a statistically significant difference from the passive control group at followup (Figure 15). Multicomponent behavioral interventions or BBT participants scored an average of 3 points lower on PSQI than passive controls.

Figure 15. Efficacy of multicomponent behavioral therapy or brief behavioral therapy in older adults: PSQI score



Sleep Outcomes

Two of three sleep outcomes improved. Sleep outcomes were reported in all multicomponent behavioral intervention and BBT efficacy trials. Improvements in sleep onset latency favored BBT over passive control in all four trials. The pooled estimate shows that multicomponent behavioral therapies or BBT reduced sleep onset latency by more than 10 minutes over passive control (Figure 16). All four trials reported total sleep time, showing no statistically significant increase when compared to passive control patients (Figure 17). Significant decreases in wake time after sleep onset were demonstrated in two trials.[70,72] The pooled estimate shows that multicomponent behavioral therapies or BBT reduced wake time after sleep onset by nearly 14 minutes compared to passive control.

In three of the four trials reporting sleep efficiency outcomes, results were statistically significant. The pooled estimate shows that older BBT participants increased their sleep efficiency more than 5 percentage points over passive control participants.

Figure16. Efficacy of multicomponent behavioral or brief behavioral therapy in older adults: sleep onset latency

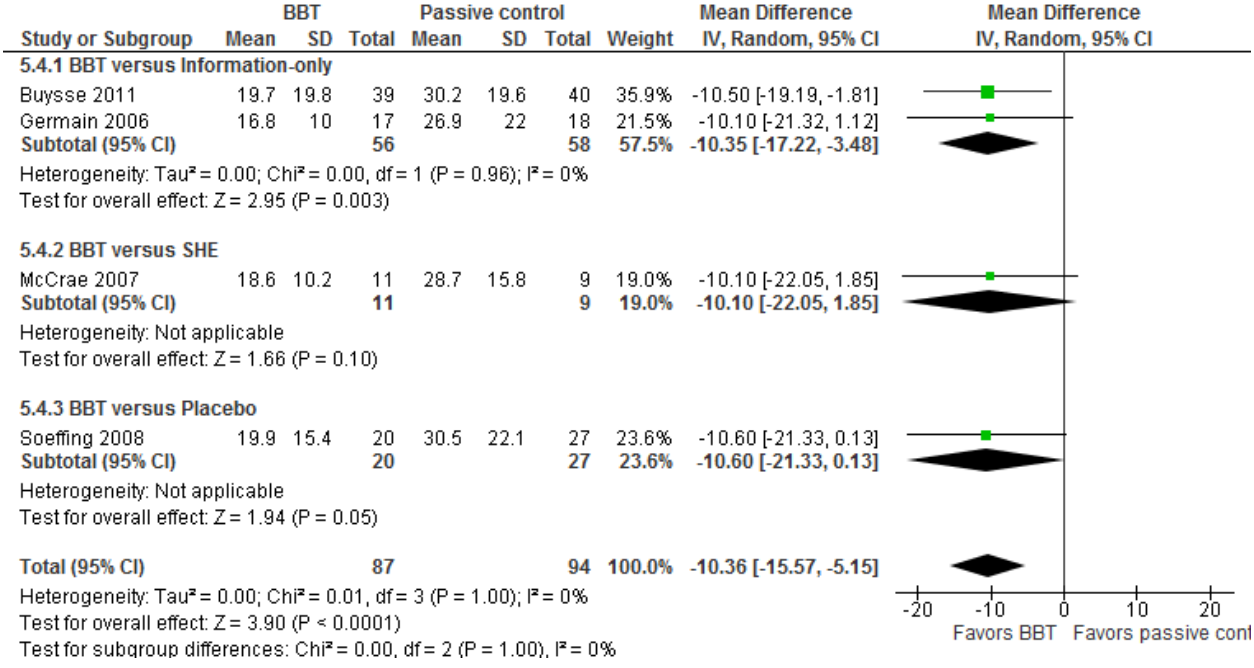
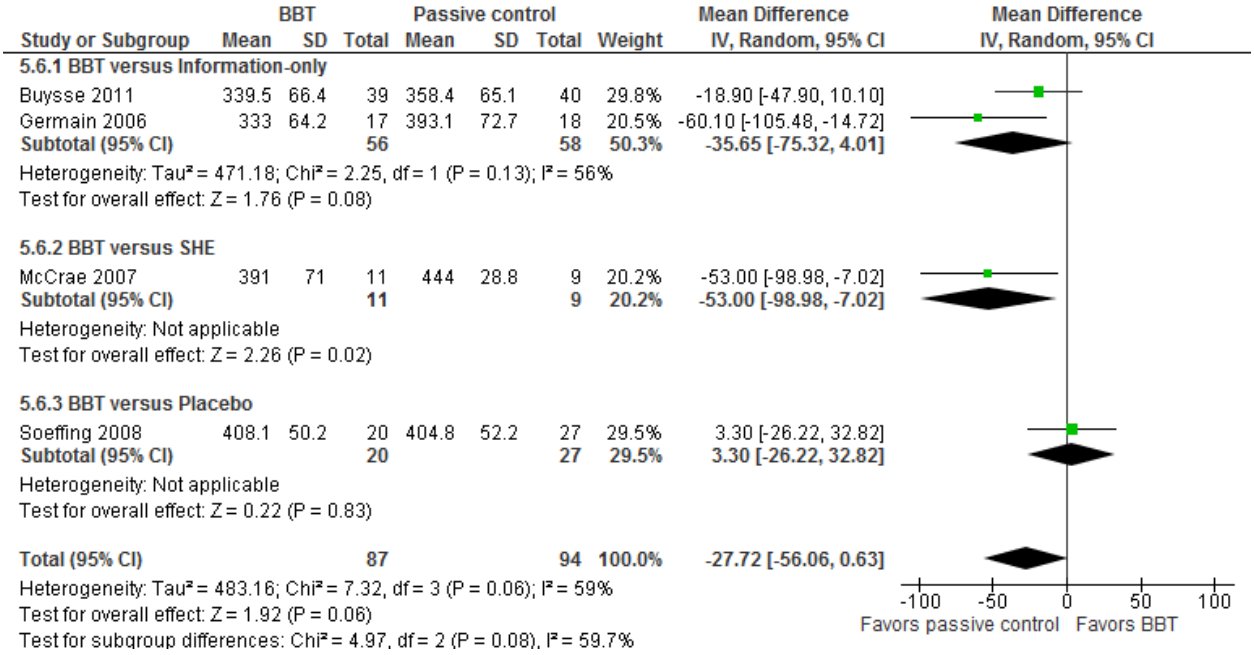


Figure 17.Efficacy of multicomponent behavioral therapy or brief behavioral therapy in older adults: total sleep time



Secondary Outcomes

One trial reported secondary outcomes. Buysee et al. reported the difference in SF-36 scores from baseline to post-treatment (4 weeks). Those in the BBT group reported less disability after 4 weeks (3.85 [SE=1.76]) and those in the passive control group reported more (-2.33 [SE=1.73]).

Adverse Effects

Specific adverse effects were not reported. Two of four trials reported study withdrawals or loss to followup (5 percent) but neither reported withdrawals or loss to followup by group.[70,71]

Efficacy of Sleep Restriction in Older Adults

Overview of Studies

We included studies as efficacy of SR if they had an active SR arm and passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We identified three trials that compared SR to a passive control in older adults (Table 9).[74-76]

All three of the studies were conducted in the United States. Studies differed in how the sleep restriction was delivered. Two studied group in-person sleep restriction[74,75] and one studied individual in-person sleep restriction.[76] The mean age across two studies reporting age was 68,[74,75] 62 percent were women,[74,75] and 97 percent were white (in the trial that reported race).[74] The mean duration of insomnia in the one study which reported it by group was 10.8 years.[74] Risk of bias was predominantly moderate.

Table 9. Efficacy of sleep restriction in older adults: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual SR vs. passive control ***(3 RCTs; N=171)***					
Global Outcomes					
Remission (ISI ≤8)	1 (94)	23 (10/44)	4 (2/50)	Favors SR RR = 5.68 [1.32 to 24.54 ARR = 18.7 NNT = 5	Insufficient (moderate study limitations, imprecise, unknown consistency)
ISI mean change	1 (94)	-	-	Favors SR MD= -5.00 [-6.94 to -3.06]	Insufficient (moderate study limitations, imprecise, unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	3 (171)	-	-	NS	Insufficient (moderate study limitations, imprecise, inconsistent)
Total sleep time, self-report, minutes	3 (171)	-	-	NS	Insufficient (study limitations, imprecise, inconsistent)
Wake time after sleep onset, self-report, minutes	3 (171)	-	-	Favors SR WMD= -24.47 [-40.98 to -7.96]	Moderate (moderate study limitations)
Sleep efficiency	3 (171)	-	-	NS	Insufficient (moderate study limitations, imprecise)
Sleep quality	1 (94)	-	-	Favors SR SMD= 0.74 [0.32 to 1.16]	Insufficient (moderate study limitations, unknown consistency)

AE=adverse effect; ARR=absolute risk reduction; CI=confidence intervals; ND=No statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; RR=risk ratio; WMD=weighted mean difference

Global Outcomes

Evidence on global outcomes was insufficient to draw conclusions because only one study reported these outcomes. It found that sleep restriction led to greater proportion of participants to achieve remission (achieving an ISI score ≤7 at followup).[74] Sleep restriction also achieve better ISI scores compared to passive comparison with a 5.68 point improvement in ISI score. This change was lower than the 7 point change associated with "response".

Sleep Outcomes

Evidence was insufficient to draw conclusions regarding most sleep outcomes. Sleep outcomes were reported in all older adult sleep restriction efficacy trials (Figures 18-21). Improvements in sleep onset latency were significantly different than passive control in one of the three trials. Pooled data shows a large range in post-intervention sleep onset latency. Due to the large range and heterogeneity, the pooled difference was not statistically significant. One trial showed a statistically significant difference in total sleep time among sleep restriction participants when compared with passive treatment controls while two did not. The pooled results did not achieve statistical significance. Two of the three trials reporting wake time after sleep onset found that sleep restriction significantly reduced wake time after sleep onset by a mean of 24.47 minutes compared to passive control. Mean sleep efficiency with sleep restriction was not significantly different than those in passive control at followup in one study. Sleep

quality was reported in one trial.[74] Mean sleep quality of those in the sleep restriction treatment group was significantly higher than those in passive control at followup.

Figure 18. Efficacy of sleep restriction among older adults: sleep onset latency

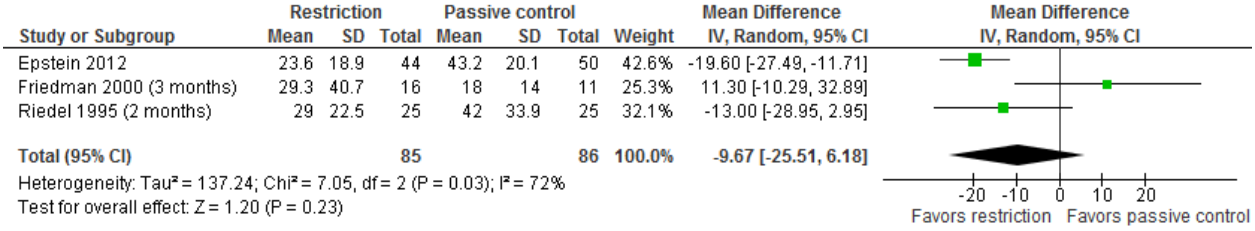


Figure 19. Efficacy of sleep restriction among older adults: total sleep time

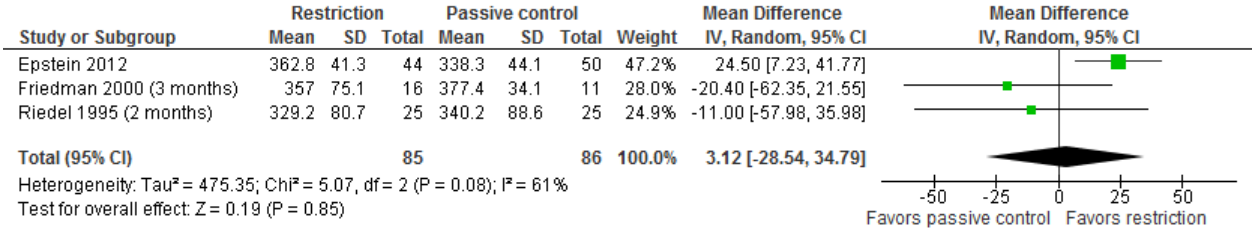


Figure 20. Efficacy of sleep restriction among older adults: wake time after sleep onset

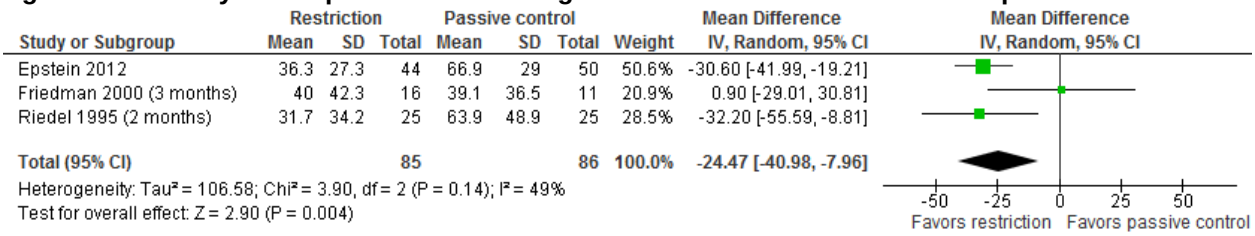
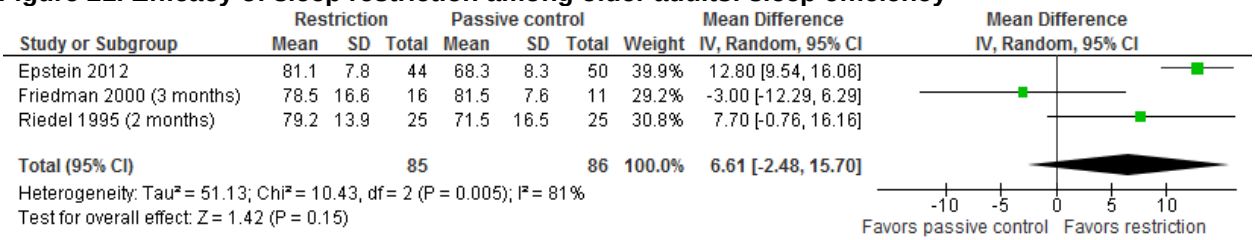


Figure 21. Efficacy of sleep restriction among older adults: sleep efficiency



Secondary Outcomes

Epstein et al. reported STAI state anxiety, STAI trait anxiety, and Geriatric Depression Scale scores for both groups and found no statistically significant differences post-treatment on STAI trait anxiety, but found statistically significant improvements in STAI state anxiety and Geriatric Depression Scale scores for the sleep restriction group when compared to passive control.[74] Friedman et al. reported Stanford Sleepiness Scale scores, but reported that they did not think the statistically significant results were clinically significant.[75]

Adverse Effects

Specific adverse effects were not reported.

Efficacy of Stimulus Control in the General Adult Population

Overview of Studies

We included studies as efficacy of stimulus control if they had an active stimulus control arm and passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We identified five RCTs that assessed the efficacy of stimulus control to treat insomnia disorder in the general adult population.[77-81] Three of the studies were conducted in the United States,[77,80,81] one was conducted in Canada,[79] and one in Scotland.[78] Studies differed in how the stimulus control was delivered. Three studied group in-person stimulus control[77,79,81] and two studied individual in-person stimulus control.[78,80] The mean age across the five studies was 51; 60 percent were women and 95 percent were white (in the trial that reported race).[80] The mean duration of insomnia in the studies which reported it was 12.4 years. We synthesized outcomes when possible (Table 10). Risk of bias was predominantly moderate to high.

Table 10. Overview and strength of evidence: efficacy of stimulus control in the general adult population

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Stimulus control vs. passive control *(5 RCTs; N=194)*					
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (47)	-	-	NS	Insufficient (moderate study limitations, imprecise)
Total sleep time, self-report, minutes	2 (47)	-	-	Favors Stimulus Control WMD= 43.19 [3.26 to 83.12]	Low (moderate study limitations, imprecise)
Wake time after sleep onset, self-report, minutes	3 (97)	-	-	NS	Insufficient (moderate study limitations, imprecise, inconsistent)
Sleep efficiency	1 (20)			NS	Insufficient (moderate risk of bias, imprecise)
Sleep quality	1 (20)	-	-	NS	Insufficient (moderate risk of bias, imprecise)

CI=confidence intervals; ND=No statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; RR=risk ratio; WMD=weighted mean difference

Global Outcomes

No global outcomes were reported in efficacy of stimulation control for insomnia disorder trials.

Sleep Outcomes

Sleep outcomes were reported in all stimulus control efficacy trials (Figures 22 and 23). Not all studies reported data in a way that permitted pooling (i.e., missing data, outcomes reported in graphical form only, only statistical tests reported). Results for one arm in one study (n=21) were reported separately due to a subgroup of participants taking sleep medication.[80] These results were not sufficiently powered to show differences in sleep outcomes.

Improvements in sleep onset latency were significantly different than passive control in one of the two trials that reported poolable data. Pooled data shows a large range in post-intervention sleep onset latency. This is due to a very large effect in one trial with a reported mean decrease in

sleep onset latency of over 65 minutes.[78] Due to the large range and heterogeneity, the pooled difference was not statistically significant.

No trials showed statistically significant differences in total sleep time among SC participants when compared to passive treatment controls. The pooled results did not achieve statistical significance. None of the three trials reporting wake time after sleep onset showed statistically significant differences. The pooled estimate was not statistically significant. Post intervention sleep efficiency was reported in one trial.[80] Mean sleep efficiency with stimulus control was not different than those in passive control at followup. Sleep quality was reported in one trial.[80] Mean sleep quality of those in the stimulus control treatment group was not different than those in passive control at followup.

Figure 22. Efficacy of stimulus control: sleep onset latency

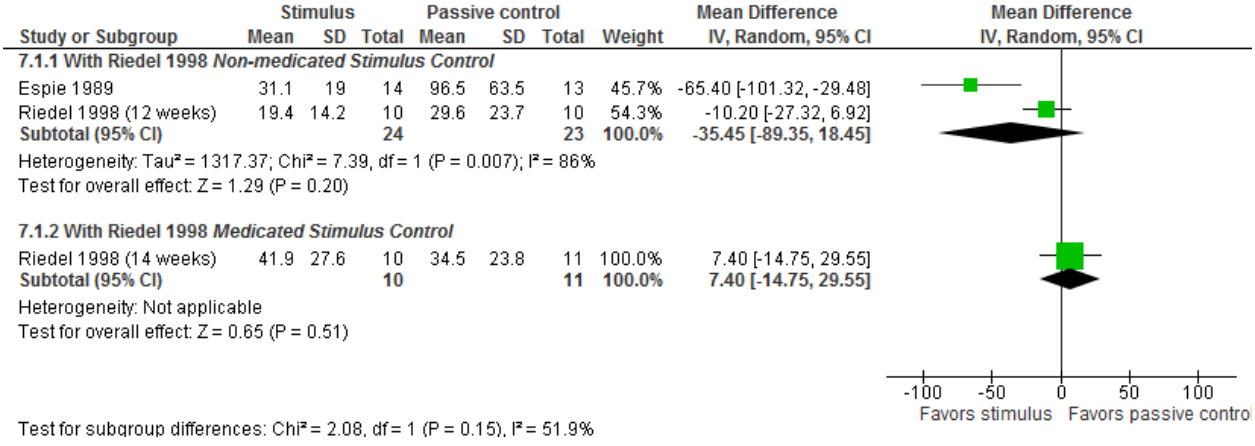
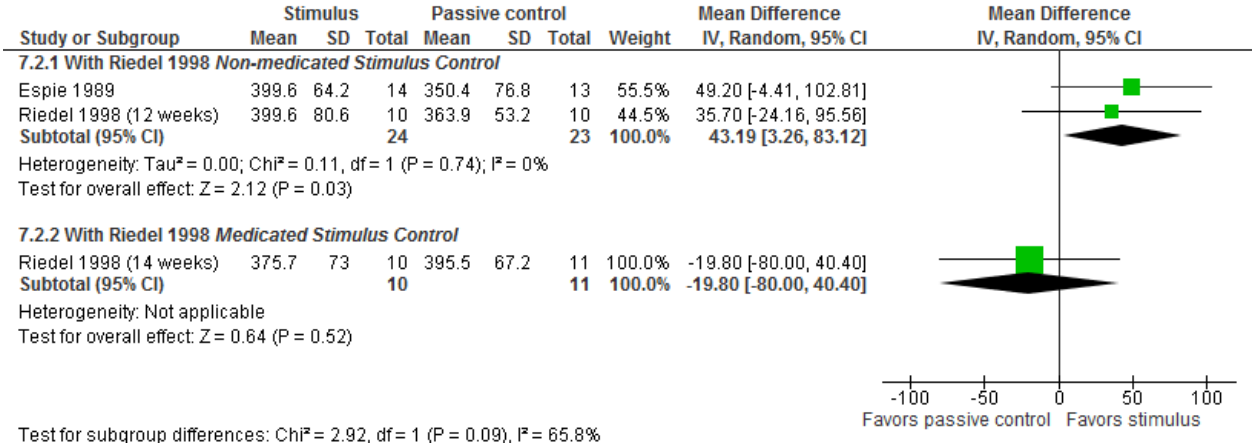


Figure 23. Efficacy of stimulus control: total sleep time



Secondary Outcomes

One study reported results for the Epworth Sleepiness Scale, the Beck Depression Inventory, and the State-Trait Anxiety Inventory.[80] No significant differences were found.

Adverse Effects

Specific adverse effects were not reported. Five trials reported withdrawals or loss to followup. Three studies did not report withdrawals or loss to followup by group.[77,78,81]

Efficacy of Stimulus Control in Older Adults

Overview of Studies

We included studies as efficacy of stimulus control if they had an active stimulus control arm and passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We identified three trials that compared stimulus control with passive control in older adults.[74,82,83] Two studies did not report data in a way that permitted pooling (Table 11).

Two of the studies were conducted in the United States[74,83] and one was conducted in Canada.[82] The mean age across studies reporting age was 69; 67 percent were women and 99 percent were white (in the trial that reported race).[74] The mean duration of insomnia in the three studies which reported it was 12.7 years. We pooled results when possible (Table 11).

Table 11. Overview and strength of evidence: efficacy of stimulus control in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Stimulus Control vs. passive control ***reporting sample size by group) (3 RCTs; N=129)***					
Global Outcomes					
Remission (ISI ≤7)	1 (94)	30 (13/44)	4 (2/50)	Favors SC RR = 7.39 [1.76 to 30.94] ARR = 25.5 NNT = 4	Insufficient (moderate study limitations, imprecise, unknown consistency)
ISI mean change	1 (94)	-	-	Favors SC MD= -5.10 [-7.02 to -3.18]	Insufficient (moderate study limitations, unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	3 (129)	-	-	NS WMD= -16.16 [-37.14 to 4.83]	Insufficient (moderate study limitations, imprecise, inconsistent)
Total sleep time, self-report, minutes	2 (113)	-	-	Favors SC WMD= 40.37 [23.47 to 57.27]	Low (study limitations)
Wake time after sleep onset, self-report, minutes	1 (94)	-	-	Favors SC MD= -26.60 [-38.11 to -15.09]	Insufficient (moderate study limitations, unknown consistency)
Sleep efficiency	1 (94)	-	-	Favors SC MD= 13.20 [9.92 to 16.48]	Insufficient (moderate study limitations, unknown consistency)
Sleep quality	1 (94)	-	-	Favors SC SMD= 0.99 [0.56 to 1.42]	Insufficient (moderate study limitations, imprecise, unknown consistency)

CI=confidence intervals; ND=No statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; RR=risk ratio; WMD=weighted mean difference

Global Outcomes

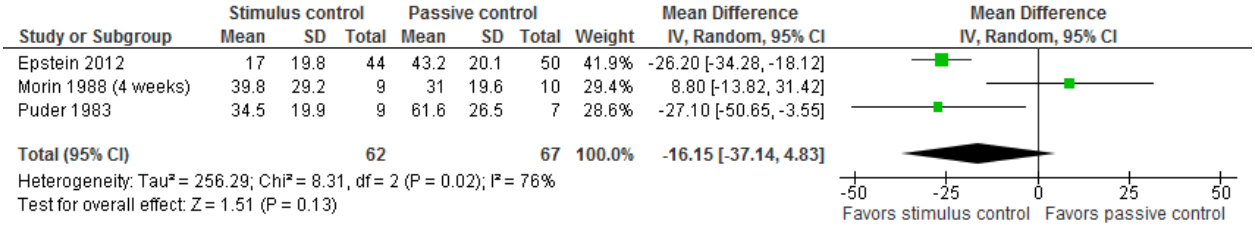
Global outcomes were reported by only one study and are therefore insufficient to draw conclusions regarding efficacy. The same study assessed insomnia remitters (achieving an ISI score ≤8 at followup).[74] Stimulus control achieved higher rates of remission compare to passive control. One study reported mean ISI scores.[74] Stimulus control resulted in a 5.10 point

improvement in ISI score compared to passive control. This difference was less than the 7 points necessary for 'response' to treatment.

Sleep Outcomes

Sleep outcomes were reported in all older adult stimulus control efficacy trials. Improvements in sleep onset latency were significantly different than passive control in two of the three trials that reported poolable data (Figure 24). Pooled data shows a large range in post-intervention sleep onset latency. Due to the large range and heterogeneity, the pooled difference was not statistically significant. One trial showed a statistically significant difference in total sleep time among stimulus control participants when compared with passive treatment controls while one did not. The pooled results achieved statistical significance with an improvement of 40.37 minutes over passive control. One trial reporting wake time after sleep onset favored stimulus control. Mean sleep efficiency with stimulus control was significantly different than those in passive control at followup in one study. Sleep quality was reported in one trial. Mean sleep quality of those in the stimulus control treatment group was significantly higher than those in passive control at followup.

Figure 24. Efficacy of stimulus control among older adults: sleep onset latency



Secondary Outcomes

Epstein et al. reported STAI state anxiety, STAI trait anxiety, and Geriatric Depression Scale scores for both groups and found no statistically significant differences post-treatment.[74] Morin and Azrin reported that they found no differences between stimulus control and passive control groups on STAI state anxiety, STAI trait anxiety, and Beck Depression Inventory from baseline to followup.[82]

Adverse Effects

Specific adverse effects were not reported. All five trials reported withdrawals or loss to followup. Three studies did not report withdrawals or loss to followup by group.

Efficacy of Relaxation Therapy Versus Passive Control in the General Adult Population

Overview of Studies

We evaluated two randomized trials comparing relaxation therapy to passive control in the general adult population (Table 12).[69,78] Participants had a mean insomnia duration of over 10 years. One trial was conducted in the United States[69] and one in the United Kingdom.[78] Both trials had a moderate risk of bias. Both trials randomized participants to relaxation therapy or passive control. Espie randomized participants to relaxation therapy, stimulus control paradoxical intention placebo, or no treatment; only two arms are discussed in this section.[78]

Woolfolk had imagery treatment, imagery treatment plus tension release, somatic focusing, progressive relaxation, or wait-list control.[69]

Table 12. Efficacy of relaxation therapy in the general adult population: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Relaxation vs. passive control ***(2 RCTs; N=42)***					
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (42)	-	-	Favors relaxation WMD= -38.65 [-73.61 to -3.69]	Low (moderate study limitations, imprecise)
Total sleep time, self-report, minutes	1 (27)	-	-	NS MD= 34.20 [-24.66 to 93.06]	Insufficient (moderate study limitations, imprecise, unknown consistency)

CI=confidence intervals; WMD=weighted mean difference

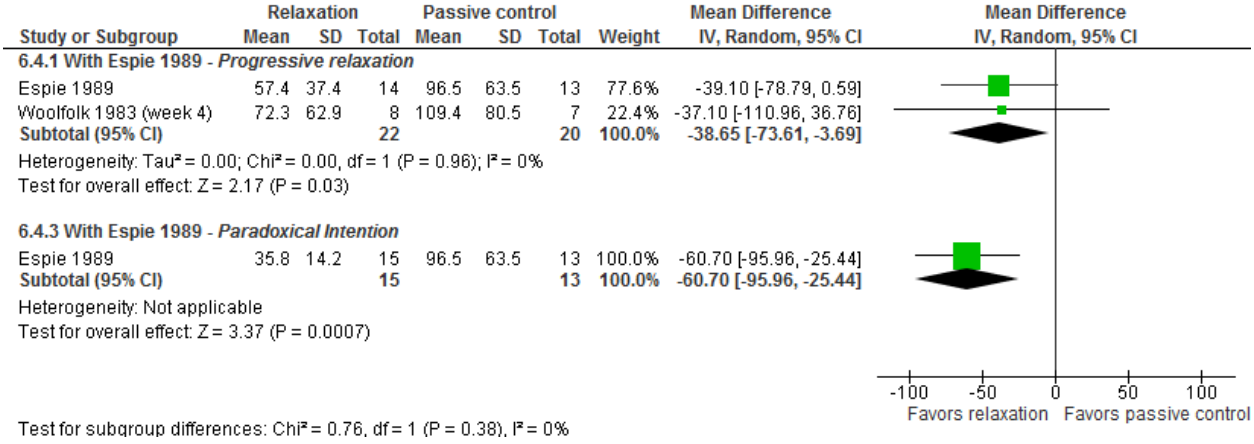
Global Outcomes

No studies of relaxation therapy versus passive control reported global outcomes.

Sleep Outcomes

Both trials reported sleep outcomes. The pooled estimate shows that relaxation therapy decreases sleep onset latency by nearly 40 minutes over passive control (Figure 25).

Figure 25. Efficacy of relaxation therapy in the general adult population: sleep onset latency



Secondary Outcomes

No trials reported secondary outcomes.

Adverse Effects

Specific adverse effects were not reported. All four trials reported withdrawals or loss to followup. None of the studies reported withdrawals or loss to followup by group.

Comparative Effectiveness of Relaxation Therapy Versus Stimulus Control in the General Adult Population

Overview of Studies

We evaluated two randomized trials comparing relaxation therapy to passive control in adults (Table 13);[78,84] no data were poolable. The two trials randomized 62 participants, the mean age was 43, and 71 percent were women. Participants had a mean insomnia duration of 13.1 years. One trial was conducted in the United States[84] and one in the United Kingdom; only two arms are discussed in this section.[78] Espie randomized participants to relaxation therapy, stimulus control paradoxical intention placebo, or no treatment. Lacks et al. randomized participants to progressive relaxation, stimulus control, paradoxical intention, or placebo control.[84] Risk of bias was moderate to high for these trials.

Table 13. Comparative effectiveness of relaxation therapy versus stimulus control in the general adult population: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Relaxation vs. stimulus control *(2 RCTs; N=62)*					
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (28)	-	-	Favors stimulus control MD: 26.30 [4.33 to 48.27]	Insufficient (moderate study limitations, imprecise)
Total sleep time, self-report, minutes	1 (28)	-	-	NS	Insufficient (moderate study limitations, imprecise, unknown consistency)

CI=confidence intervals; WMD=weighted mean difference

Global Outcomes

No studies of relaxation therapy versus passive control reported global outcomes.

Sleep Outcomes

Both trials reported sleep outcomes; however, only Espie reports analyzable data.[78] Sleep onset latency decreases with stimulus control compared to relaxation therapy with a statistically significant mean difference of more than 26 minutes.

Secondary Outcomes

No trials reported secondary outcomes.

Adverse Effects

Specific adverse effects or withdrawals by group were not reported.

Comparative Effectiveness of Psychologic Treatments

We identified nine additional studies that compared different psychological interventions. The lack of similar comparisons yielded insufficient evidence to draw conclusions about the comparative effectiveness of different psychological interventions.

None of these studies included comparisons similar to other studies, so they were analyzed only descriptively. Two studied delivery modes of CBT-I. Bastien et al.[85] compared individual-, group-, and telephone-delivered CBT-I. Mimeault et al. included two arms that compared self-help CBT-I to self-help CBT-I with professional guidance.[54] Rybarczyk et al. compared two types of CBT-I (self-help versus therapist led) in older participants, most of whom had comorbidities.[86]

Edinger et al. randomized 75 participants to CBT-I, relaxation training, or quasi-desensitization (they call this group the placebo group).[87] Similarly, Lichstein, et al. used a quasi-desensitization control in studying relaxation and stimulus control.[88] We did not classify these trials with the efficacy trials because the description of quasi-desensitization placebo was not similar to the passive controls we grouped into the efficacy section. Similarly, Pech et al. compared two multicomponent programs (both contained sleep hygiene education, stimulus control, and progressive relaxation; the two groups additionally got either cognitive therapy or problem solving therapy[89] to stress management programs. Rybarczyk et al. randomized older participants to participants to CBT-I or stress management.[90]

Two studies assessed the adjunctive efficacy of certain components. Jansson-Fromark et al. assessed the adjunctive efficacy of a constructive worry program to a multicomponent behavioral treatment.[91] Riley et al. studied the adjunctive efficacy of behavioral prompts as adjunctive functions in a computer device provided to all participants.[92]

Efficacy and Comparative Effectiveness of Bright Light Therapy

We identified several trials that compared different exposures to bright light for insomnia disorder. Evidence for all populations and outcomes was insufficient to draw conclusions because no two studies analyzed similar comparisons.

One comparativeness effectiveness trial looked at exposure to bright versus dim light conditions. Lack et al.[93] randomized 20 participants to (2500 lux) or di, red light (100 lux) and reported on 16 completers. The mean age of completers was 29, 69 percent were women, and they had an average insomnia duration of 8.2 years. No global outcomes were reported. There were no statistical differences between groups on any sleep outcome.

Two comparative effectiveness trials looked at different bright light therapies in the treatment of older adults with insomnia. [94,95] Friedman et al. randomized older participants to bright (~4,000 lux) or dim light. Friedman et al. randomized 61 participants but reports results on 51 completers only. Mean age was 64.0 and 69 percent were women. Friedman et al. reported an insomnia duration of 14.9 years. Kirisoglu et al. randomized older adults to 20 or 45 minutes of daily exposure to 10,000 lux for 60 days.[94] Both studies report only sleep outcomes. Changes in sleep outcomes were not significantly different between groups in Friedman et al. found that mean sleep onset latency and total sleep time were significantly different at both 3 and 6 months post-treatment. Longer exposure (45 minutes compared with 20 minutes daily) resulted in shorter sleep latencies and longer total sleep times.

Efficacy of Pharmacologic Treatment

Key Points

- Nonbenzodiazepine hypnotics have low to moderate strength evidence for efficacy on global and a wide range of sleep outcomes in the general adult population. Improvements over placebo in sleep outcomes were higher with eszopiclone and zolpidem than

zaleplon. Results for adverse effects were mixed with few differences compared to placebo.

- Eszopiclone and zolpidem had some evidence of improved outcomes in older adults. Low strength evidence shows that eszopiclone improved one global outcome by a minimum important difference and improved several sleep outcomes, but not sleep onset latency. Evidence on adverse effects was insufficient. Low strength evidence shows that zolpidem improved sleep onset latency had higher adverse effects. Evidence on other outcomes was insufficient.
- Prolonged release melatonin improved one sleep outcome in the general adult population; low strength evidence shows that sleep onset latency improved by a mean of 6 minutes; evidence for all other outcomes and adverse effects were insufficient.
- Ramelteon was similar to placebo with respect to three sleep outcomes in the general adult population. There was no difference in sleep onset latency, total sleep time, or wake time after sleep onset. Low strength evidence shows that sleep quality improved less with ramelteon than with placebo. Withdrawals were higher with ramelteon (low strength evidence), but withdrawals for adverse effects and number of patients with more than one adverse effect were similar in both groups (low and moderate strength evidence, respectively).
- Low strength evidences shows ramelteon was similar to placebo with respect to two sleep outcomes in older adults, but did improve sleep onset latency by an average of 6 minutes. Low strength evidence shows no difference in adverse effects between ramelteon and placebo.
- Very few benzodiazepine trials met eligibility criteria. Data was insufficient to assess any global, sleep, or adverse effect outcomes in the general adult or older adult populations.
- Data on antidepressants (trazodone and doxepin) in the general adult population was insufficient for global and sleep outcomes. No differences in proportion of participants in the doxepin trial with more than one adverse effect were demonstrated. Evidence was insufficient for other adverse effects.
- Data on antidepressants (doxepin) in older adults was insufficient for global and sleep outcomes. Low strength evidence shows no differences in adverse effects.

We identified 32 RCTs that evaluated pharmacologic treatments for insomnia disorder in the general adult population (Table E) and in older adults (Table F). We found the most data on the newer FDA-approved drugs.

Efficacy of Nonbenzodiazepine Hypnotics in the General Adult Population

We identified fourteen RCTs that assessed the efficacy of three nonbenzodiazepine hypnotics commonly used to treat insomnia disorder in the United States (eszopiclone [Lunesta], zaleplon [Sonata], and zolpidem [Ambien] (Table 14).

Table 14. Overview and strength of evidence: efficacy of nonbenzodiazepine hypnotics

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Eszopiclone 2-3 mg vs. placebo ***(3 RCTs; N=1,929)***					

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Global Outcomes					
Remission from Insomnia disorder based on ISI	1 (825)	50 (272/547)	19 (52/278)	Favors eszopiclone RR= 2.66 [2.05 to 3.44] ARR= 0.31 [0.25 to 0.37] NNT= 4	Low (moderate study limitations and unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	3 (1,820)	-	-	Favors eszopiclone WMD= -19.1 [-24.1 to -14.1]	Moderate (moderate study limitations)
Total sleep time, self-report, minutes	3 (1,820)	-	-	Favors eszopiclone WMD= 44.8 [35.4 to 54.2]	Moderate (moderate study limitations)
WASO, self-report, minutes	3 (1,820)	-	-	Favors eszopiclone WMD= -10.8 [-19.8 to -1.70];	Low (moderate study limitations and inconsistency [I^2=70%])
Sleep quality	2 (992)	-	-	Favors eszopiclone SMD= 0.47 [0.32 to 0.61]	Moderate (moderate risk of bias)
Adverse Effects					
Overall withdrawals	3 (1,927)	33 (450/1352)	41 (236/575)	Greater with placebo RR= 0.81 [0.66 to 1.00]; ARR= -0.06 [-0.17 to 0.04]	Low (moderate moderate study limitations and imprecise)
Withdrawals due to adverse events	3 (1,927)	9 (127/1352)	6 (36/575)	NS	Low (moderate moderate study limitations and imprecise)
Participants with ≥1 adverse event	2 (1,616)	79 (896/1141)	64 (303/475)	Greater with eszopiclone RR= 1.21 [1.08 to 1.36] ARR= 0.14 [0.07 to 0.20] NNH= 7	Moderate (moderate study limitations)
Zaleplon 5-20 mg vs. placebo (2 RCTs; N=973)					
Global Outcomes					
Not reported					Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (209)	-	-	Favors zaleplon with 10 mg dose MD= -9.90 [-19.45 to -0.35] NS with 5 mg dose	Insufficient (moderate moderate study limitations, imprecise, and unknown consistency)
Total sleep time, self-report, minutes	2 (822)	-	-	NS (unable to pool data)	Low (moderate moderate study limitations and imprecise)
Sleep quality, *Improved sleep quality, self-report*	2 (879)	57 (376/656)	48 (108/223)	Favors zaleplon RR= 1.19 [1.02 to 1.38] ARR= 0.09 [0.01 to 0.17] NNT= 11	Moderate (moderate study limitations)
Adverse Effects					
Overall withdrawals	2 (971)	12 (85/726)	8 (20/245)	NS	Low (moderate moderate study limitations and imprecise)
Withdrawals due to adverse events	2 (965)	4 (29/720)	2 (6/245)	NS	Low (moderate moderate study limitations and

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
					imprecise)
Participants with ≥1 adverse event	2 (965)	71 (510/720)	73 (178/245)	NS	Moderate (moderate moderate study limitations)
Zolpidem 10-15 mg vs. placebo (4 RCTs; N=704)					
Global Outcomes					
NR					Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (255)	-	-	Favors zolpidem WMD = -12.8 [-21.5 to -4.2]	Moderate (moderate moderate study limitations)
Total sleep time, self-report, minutes	4 [b]	-	-	Inconsistent results	Low (moderate study limitations ,imprecise and consistency)
Sleep quality, *Improved sleep quality, self-report*	3 (557)	69 (200/289)	49 (130/268)	Favors zolpidem RR=1.40 [1.20 to 1.65] ARR= 0.21 [0.09 to 0.33] NNT= 5	Moderate (moderate study limitations)
Adverse Effects					
Overall withdrawals	4 (704)	14 (52/381)	10 (31/323)	NS	Low (moderate study limitations and imprecise)
Withdrawals due to adverse effects	4 (703)	6 (23/380)	2 (6/323)	Greater with zolpidem RR = 2.65 [1.12 to 6.28] ARR= 0.04 [0.02 to 0.07] NNH= 25	Moderate (moderate study limitations)
Participants with ≥1 adverse effect	4 (698)	68 (256/376)	67 (215/322)	NS	Moderate (moderate study limitations)
Zolpidem 10 mg "as needed" vs. placebo (3 RCTs; N=607)					
Global Outcomes					
Clinical Global Impression – "Much or very much improved"	1 (243)	54 (67/124)	24 (29/119)	Favors zolpidem RR= 2.22 [1.55 to 3.16] ARR= 0.30 [0.18 to 0.41] NNT= 4	Low (moderate study limitations, imprecise, unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	2 (355)	-	-	Favors zolpidem WMD = -14.8 [-23.4 to -6.2]	Moderate (moderate study limitations)
Sleep onset latency, self-report, mean change, minutes	1 (245)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Total sleep time, self-report, minutes	2 (355)	-	-	Favors zolpidem WMD = 48.1 [34.8 to 61.5]	Moderate
Total sleep time, self-report, mean change, minutes	1 (245)			NS	Insufficient (moderate study limitations, imprecise, unknown consistency)
Wake time after	2 (437)	-	-		Low (moderate risk

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
sleep onset, self-report, minutes				Inconsistent results	of bias, imprecise, and Inconsistent)
Wake time after sleep onset, self-report, mean change, minutes	1 (245)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Adverse Effects					
Overall withdrawals	3 (607)	13 (39/304)	13 (38/303)	NS	Low (moderate study limitations, imprecise)
Withdrawals due to adverse effects	3 (607)	4 (12/304)	1 (4/303)	NS	Insufficient (study limitations, very imprecise)
Participants with ≥1 adverse effects	1 (245)	19 (23/124)	15 (18/121)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Zolpidem 3.5 mg SL vs. placebo (1 RCT; N=295)					
Sleep Outcomes					
Sleep onset latency, self-report, minutes*, post middle of the night*	1 (295)			4 week average estimates zolpidem 38 minutes vs. placebo 56 minutes (P<0.0001)	Insufficient (moderate study limitations and unknown consistency)
Total sleep time, self-report, minutes*, post middle of the night*	1 (295)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Wake time after sleep onset, self-report, minutes, *post middle of the night*	1 (295)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Sleep quality, *Scale from 1 (extremely poor to 9 excellent)*	1 (295)	-	-	SMD 0.38 [0.15 to 0.61]	Insufficient (moderate study limitations and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (295)	8 (12/150)	6 (8/144)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Withdrawals due to adverse effects	1 (295)	0 (0/150)	<1 (1/144)	NS	Insufficient (moderate study limitations, imprecise, and

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
					unknown consistency)
Zolpidem 12.5 mg ER vs. placebo (1 RCT; N=1,018)					
Global Outcomes					
Clinical Global Impression – "Much or very much improved"	1 (1,016)	85 (567/667)	48 (168/349)	Favors zolpidem ER RR= 1.77 [1.58 to 1.98] ARR= 0.37 [0.31 to 0.43] NNT= 3	Low (unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, mean change, minutes	1 (1,018)			Greater with zolpidem ER (graphically displayed)	Insufficient (unknown consistency, unknown precision)
Total sleep time, self-report, mean change, minutes	1 (1,018)			Greater with zolpidem ER (graphically displayed)	Insufficient (unknown consistency, unknown precision)
Wake time after sleep onset, self-report, mean change, minutes	1 (1,018)			Greater with zolpidem ER (graphically displayed)	Insufficient (unknown consistency, unknown precision)
Adverse Effects					
Overall withdrawals	1 (1,018)	36 (238/669)	48 (167/349)	Greater with placebo RR= 0.74 [0.64 to 0.86]; ARR= -0.12 [-0.19 to -0.06]	Low (unknown consistency)
Withdrawals due to adverse effects	1 (1,018)	8 (55/669)	5 (16/349)	Greater with zolpidem ER RR = 1.79 [1.04 to 3.08] ARR= 0.04 [0.01 to 0.07] NNH= 25	Low (unknown consistency)
Participants with ≥1 adverse effect	1 (1,018)	63 (423/669)	51 (179/349)	Greater with zolpidem ER RR = 1.23 [1.10 to 1.39] ARR= 0.12 [0.06 to 0.018] NNH= 9	Low (unknown consistency)

AR=absolute risk reduction; CI=confidence intervals; ER=extended release; ND=No statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; NR=not reported; RR=risk ratio; SL=sublingual; WMD=weighted mean difference

Efficacy of Eszopiclone (Brand Name Lunesta)

Overview of Studies

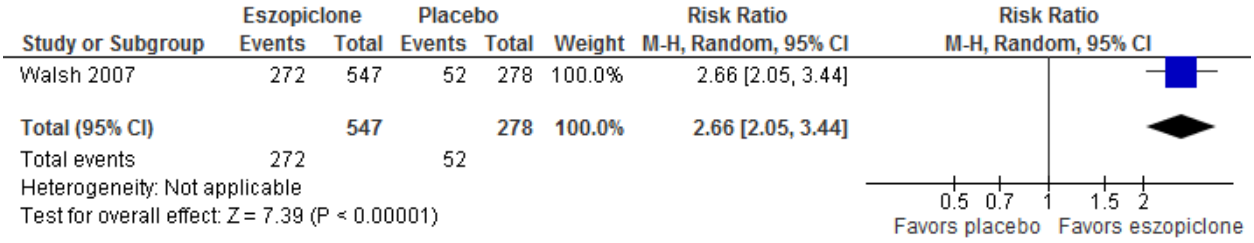
We identified three eligible RCTs that analyzed the efficacy of eszopiclone[96-98] (Table 14). The three RCTs randomized 1,929 participants with a mean age of 49; 63 percent were women. Most participants were white in the trials that reported race/ethnicity. All trials were conducted in the United States. Participants were randomized to 2 mg[98] or 3 mg eszopiclone.[96-98] One trial lasted 6 weeks[98] and two lasted 6 months.[96,97] All trials reported industry sponsorship and had moderate risk of bias.

Global Outcomes

Only Walsh et al. (n=825) reported clinically meaningful improvement in sleep based on ISI scores (Figure 26).[97] Low-strength evidence shows that compared with placebo, eszopiclone

more often resulted in remission or no clinically significant insomnia, indicated by an ISI score <7 at endpoint (50 percent vs. 19 percent). The mean difference in ISI scores at 12 weeks of was -4.5 points (95% CI, -5.2 to -3.8) but this difference did not reach our minimum important difference of 7 points, indicating 'responder' to treatment.

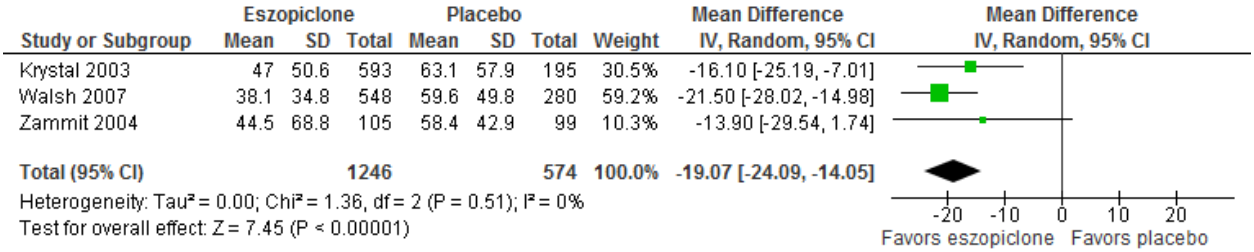
Figure 26. Efficacy of eszopiclone: remitters



Sleep Outcomes

Eszopiclone reduced sleep onset latency by 19 minutes and increased TST by 45 minutes compared to placebo (Figure 27). However, mean sleep onset latency remained above the 30 minute threshold indicating 'no insomnia' in both groups in all three trials. Strength of evidence for both outcomes was moderate. Moderate strength of evidence also showed improvement in sleep quality with eszopiclone versus placebo. Low-strength evidence showed that eszopiclone decreased wake time after sleep onset more than placebo, but there was substantial heterogeneity between trials (I^2 = 70 percent). Within the two 6-month trials, Walsh et al.[97] reported greater improvement in wake time after sleep onset with eszopiclone compared with placebo (mean difference of 18 minutes) and Krystal et al.[96] reported eszopiclone was not more effective than placebo.

Figure 27. Efficacy of eszopiclone: sleep latency, minutes



Secondary Outcomes

Secondary outcomes were rarely reported. Walsh et al. found that eszopiclone led to larger improvements in SF-36 domains of physical functioning, vitality, and social functioning than placebo.[97]

Adverse Effects

All three trials reported adverse effects. Withdrawal for any reason was higher with placebo than eszopiclone (41 percent vs. 33 percent). Withdrawals due to adverse effects did not significantly differ between groups (9 percent vs. 6 percent). Strength of evidence was low for both outcomes. A higher percentage of participants reported at least one adverse effect with eszopiclone than placebo (76 percent vs. 60 percent) (moderate strength of evidence). Krystal et

al. reported a higher rate of serious adverse effects with eszopiclone than with placebo (3 percent vs. 1 percent) at 6 months.[96] Neither 6-month trial reported evidence of tolerance or withdrawal symptoms.[96,97] Specific adverse effects associated with eszopiclone use were somnolence (9 percent vs. 3 percent for placebo), unpleasant taste (23 percent vs. 3 percent), and myalgia (9 percent vs. 4 percent).

Efficacy of Zaleplon (Brand Name Sonata)

Overview of Studies

We evaluated two 4-week RCTs that compared zaleplon with placebo.[99,100] The two trials randomized 973 participants, the mean age was 42, and 61 percent were women. Participants were overwhelmingly white. One trial was conducted in the United States[100] and one was conducted in Canada and Europe.[99] Participants were randomized to 5, 10, or 20 mg doses. Both trials reported industry sponsorship and had moderate risk of bias.

Global Outcomes

Neither of the zaleplon trials reported global outcomes.

Sleep Outcomes

Fry et al. reported that zaleplon 10 mg but not 5 mg reduced mean sleep onset latency versus placebo (Figure 28).[100] Elie et al. reported a lower median sleep onset latency with zaleplon 10 and 20 mg doses than placebo over the 4-week study period (Figure 29).[99] Both trials reported that zaleplon did not consistently improve median total sleep time or sleep quality over placebo at 4 weeks. Participants randomized to any zaleplon dose were more likely than placebo participants to report improved sleep quality at week 4 (57 percent vs. 48 percent) (moderate strength of evidence).[99,100] Individually, zaleplon doses of 5 and 20 mg, but not 10 mg, were superior to placebo in improving sleep quality at week 4 (57 percent vs. 48 percent and 60 percent vs. 48 percent, respectively).

Figure 28. Efficacy of zaleplon: subjective sleep latency, minutes

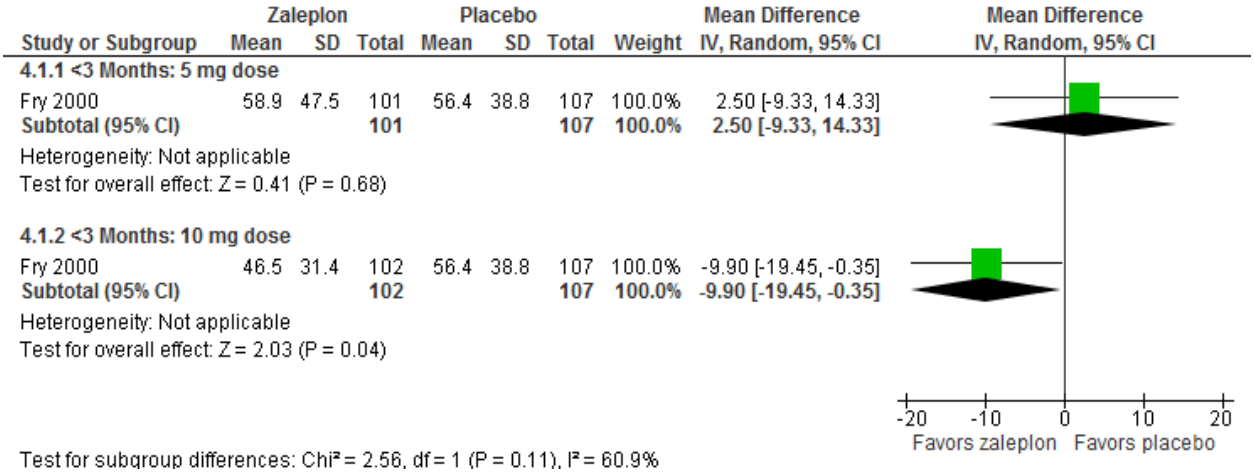
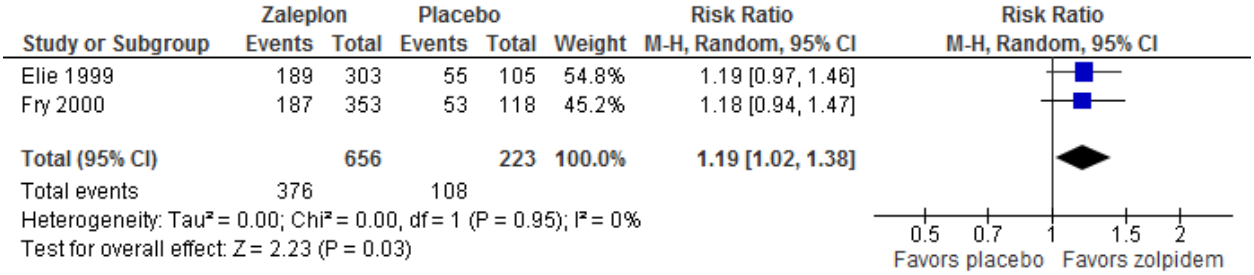


Figure 29: Efficacy of zaleplon: sleep quality, participants reporting Improvement



Secondary Outcomes

No secondary outcomes were reported in zaleplon trials.

Adverse Effects

Adverse effects were reported in all trials. Low-strength evidence shows that zaleplon at any dose compared with placebo did not increase withdrawals for any reason (12 percent vs. 8 percent) or withdrawals due to adverse effects (4 percent vs. 2 percent). Moderate-strength evidence shows that the proportion of participants reporting at least one adverse event did not differ between the zaleplon and placebo groups (71 percent vs. 73 percent). No individual adverse effect was greater with zaleplon than placebo. Neither trial reported evidence of tolerance or withdrawal symptoms. No RCTs evaluated long-term efficacy or harms (1 year or longer) of zaleplon.

Zolpidem (Brand Name Ambien)

Overview of Studies

We identified four eligible RCTs that compared zolpidem with placebo.[99-102] The four trials lasted between 4 and 5 weeks. Among the 704 randomized, the mean age was 43, and 58 percent were women. Participants were overwhelmingly white. Three trials were conducted in the United States[100-102] and one in Europe and Canada.[99] Two trials evaluated a 10 mg dose[99,100] and two trials evaluated 10 and 15 mg doses.[101,102] Risk of bias was moderate in all trials. Three trials reported industry sponsorship. Sponsorship was unclear in one trial.[102]

Global Outcomes

No zolpidem trial reported global outcomes.

Sleep Outcomes

Moderate strength evidence showed that zolpidem 10 mg reduced sleep onset latency by 13 minutes compared with placebo in two trials reporting poolable data (Figure 30).[100,102] The 15 mg dose in Scharf et al. was better than placebo (28 minutes vs. 48 minutes reduction in sleep onset latency).[102] In the trials not pooled due to variations in how they reported outcomes, Lahmeyer et al. reported improvement in sleep onset latency at 4 weeks compared with placebo (change from baseline approximately -30 minutes vs. -10 minutes).[101] Elie reported that zolpidem was no more effective than placebo in improving sleep onset latency at week 4.[99] Moderate strength evidence shows that zolpidem improved sleep quality or the proportion of participants "getting a better night's sleep" more than placebo (69 percent vs. 49 percent) (Figure 31). Lahmeyer et al. reported that 10 and 15 mg zolpidem improved clinical global impression of

sleep quality over placebo (both 84 percent vs. 49 percent).[101] Zolpidem did not consistently improve total sleep time or sleep quality compared with placebo across trials.

Figure 30. Efficacy of zolpidem: subjective sleep latency, minutes

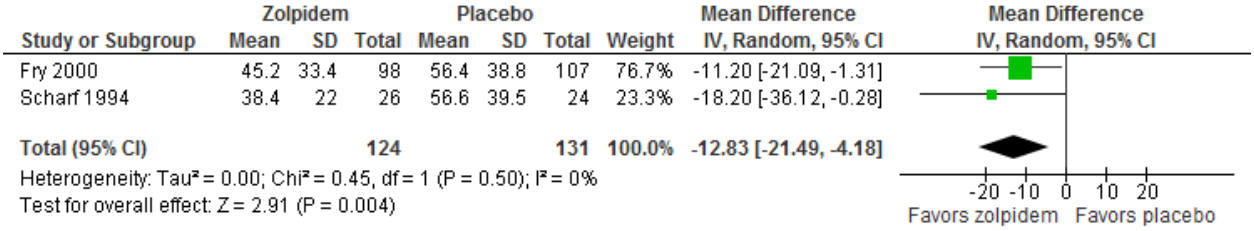
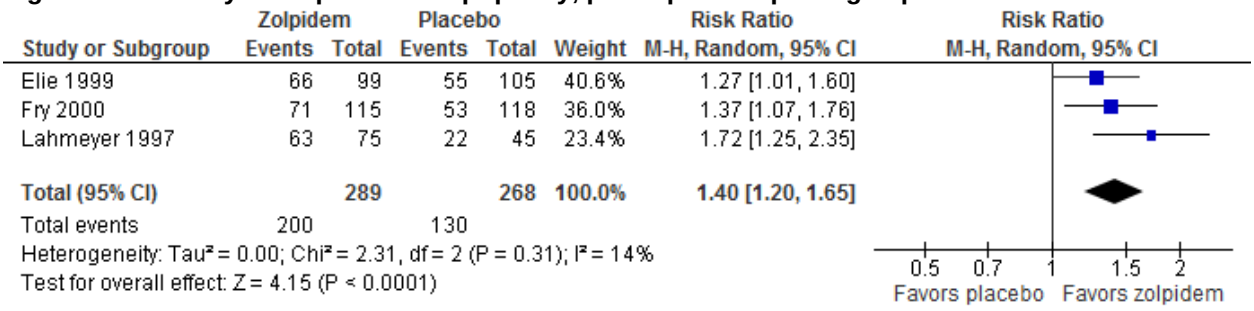


Figure 31. Efficacy of zolpidem: sleep quality, participants reporting Improvement



Secondary Outcomes

No secondary outcomes were reported in zolpidem trials.

Adverse Effects

Study withdrawals for any reason (14 percent vs. 10 percent) or reporting of at least one adverse effect (68 percent vs. 67 percent) were not greater with zolpidem than with placebo. Strength of evidence was low and moderate, respectively. Moderate-strength evidences suggests that zolpidem resulted in more withdrawals due to an adverse effects than placebo (6 percent vs. 3 percent). Among adverse effects reported, somnolence was greater with zolpidem than placebo (10 percent vs. 3 percent). Frequencies of other adverse effects were comparable to placebo. Two trials reported a higher incidence of withdrawal symptoms and rebound insomnia following discontinuation of zolpidem compared with placebo.[99,100] Incidence of withdrawal symptoms and rebound insomnia did not differ between treatment groups in the other two trials.[101,102]

Zolpidem 'As Needed'

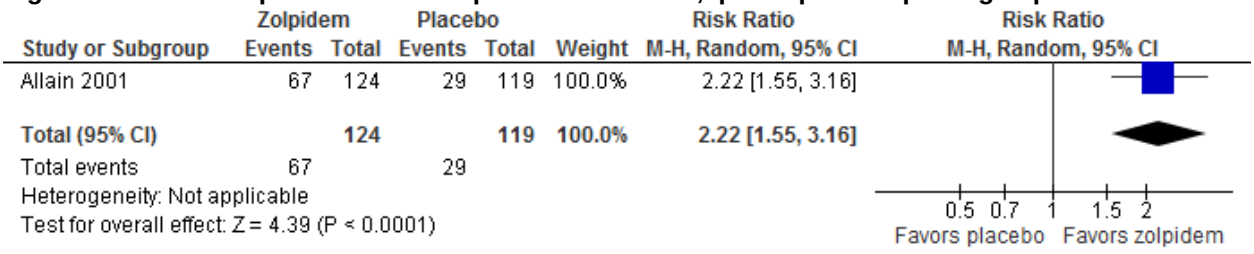
Overview of Studies

We identified three eligible RCTs that compared zolpidem 'as needed' with placebo.[103-105] No trial lasted longer than 12 weeks; one lasted 12 weeks[104] one 8 weeks,[105] and one 4 weeks.[103] Among the 607 randomized, the mean age was 44, and 73 percent were women. Perlis et al. reported more women in the placebo arm (81 percent) than the zolpidem arm (69 percent).[104] Most participants in the one trial that reported race/ethnicity were white.[104] Two trials were conducted in the United States[104,105] and one in France.[103] Participants were randomized to 10 mg zolpidem or placebo 'as needed' in all trials. Two trials reported industry sponsorship.[103,104] Sponsorship was unclear in one trial,[105] Risk of bias was moderate for all trials.

Global Outcomes

Only Allain et al. reported a global outcome (Figures 32).[103] Low-strength evidence showed that zolpidem "as needed" led to "much or very much improvement" as rated by the clinician (CGI) more often than placebo (54 percent vs. 24 percent).

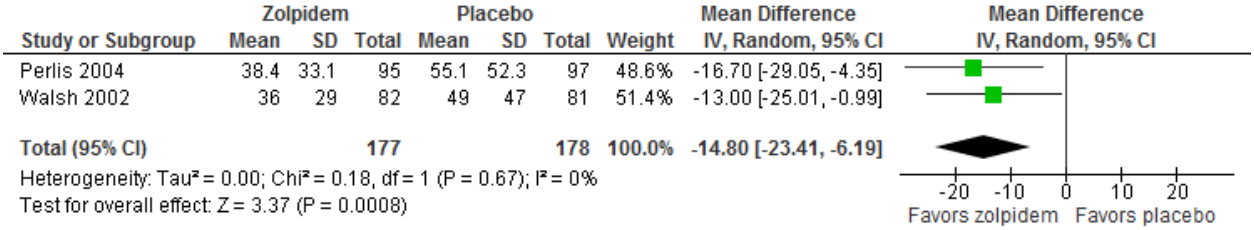
Figure 32: Global improvement of zolpidem 'as needed,' participants reporting improvement



Sleep Outcomes

In two trials reporting poolable data, moderate-strength evidence showed that zolpidem 10 mg 'as needed' reduced sleep onset latency by 15 minutes (Figure 33) and increased total sleep time by 48 minutes compared to placebo (95% CI, 35 to 62) on nights when medication was taken.[104,105] Allain et al. reported no significant improvements versus placebo in sleep onset latency, total sleep time, wake time after sleep onset, and number of awakenings after sleep onset with zolpidem 'as needed.'[103] Compared with placebo, Perlis et al. reported significant improvements with zolpidem 'as needed' in wake time after sleep onset (-22 minutes (95% CI, -37 to -9) and number awakenings after sleep onset.[104]

Figure 33: Subjective sleep latency, minutes: zolpidem 'as needed' versus placebo



Secondary Outcomes

Zolpidem 10 mg 'as needed' led to greater improvement in the Medical Outcomes Sleep (MOS) questionnaire compared with placebo (SMD 0.48 [95% CI, 0.22 to 0.74]); treatment effects did not differ for any SF-36 domain.[103]

Adverse Effects

Zolpidem 'as needed' and placebo were similar in the number of study withdrawals for any reason (13 percent vs. 13 percent) or withdrawals due to adverse effect (4 percent vs. 1 percent). The strength of evidence was low and insufficient, respectively. Adverse effects associated with zolpidem 'as needed' included anxiety, somnolence, mood alterations, hallucinations, and depression. We identified no RCTs that evaluated the long-term effects (1 year or longer) of zolpidem 'as needed.'

Efficacy of Zolpidem, Special Formulations: Zolpidem Sublingual

Overview of Studies

One 4-week trial compared low-dose zolpidem sublingual 3.5 mg 'as needed' with placebo in participants with difficulty returning to sleep after middle-of-the-night awakenings.[106] Among the 295 randomized, the median age was 43, 68 percent were women, and 64 percent were white. The trial was industry sponsored and conducted in the United States. Risk of bias was moderate.

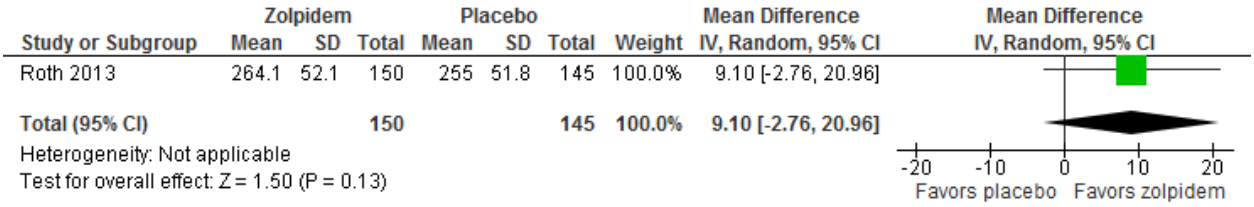
Global Outcomes

No global outcomes were reported for zolpidem SL.

Sleep Outcomes

Zolpidem sublingual reduced sleep onset latency compared with placebo (38 vs. 56 minutes) (Figure 34).[106] Roth et al., also reported improvements in wake time after sleep onset, and sleep quality (dosing nights only) with zolpidem sublingual during nights when medication was taken.[106] Zolpidem sublingual did not improve total sleep time following middle of the night awakening over placebo at 4 weeks. The strength of evidence was insufficient for all outcomes.

Figure 34. Total sleep time following middle of the night awakening, minutes: zolpidem sublingual 'as needed' versus placebo



Secondary Outcomes

No secondary outcomes were reported for zolpidem sublingual.

Adverse Effects

Withdrawals for any reason (8 percent vs. 6 percent) were not different with zolpidem sublingual and placebo. A similar number of participants withdrew due to an adverse effects (0 percent vs. <1 percent) and reported at least one adverse effect (19 percent each).[106] The strength of evidence was insufficient for both outcomes. Specific adverse effects associated with zolpidem sublingual were headache (3 percent) and nausea and fatigue (1 percent each). Nasopharyngitis (3 percent) was the most commonly reported adverse effect with placebo. We identified no trials that evaluated long-term efficacy and harms (1 year or longer) for zolpidem sublingual.

Efficacy of Zolpidem, Special Formulations: Zolpidem Extended Release

Overview of Studies

Krystal et al., compared zolpidem extended-release 12.5 mg taken at least 3 nights per week with placebo over 24 weeks.[107] Among the 1018 randomized, the mean age was 46; 61 percent

were women, and 65 percent were white. The trial was industry sponsored and conducted in the United States. Risk of bias was low.

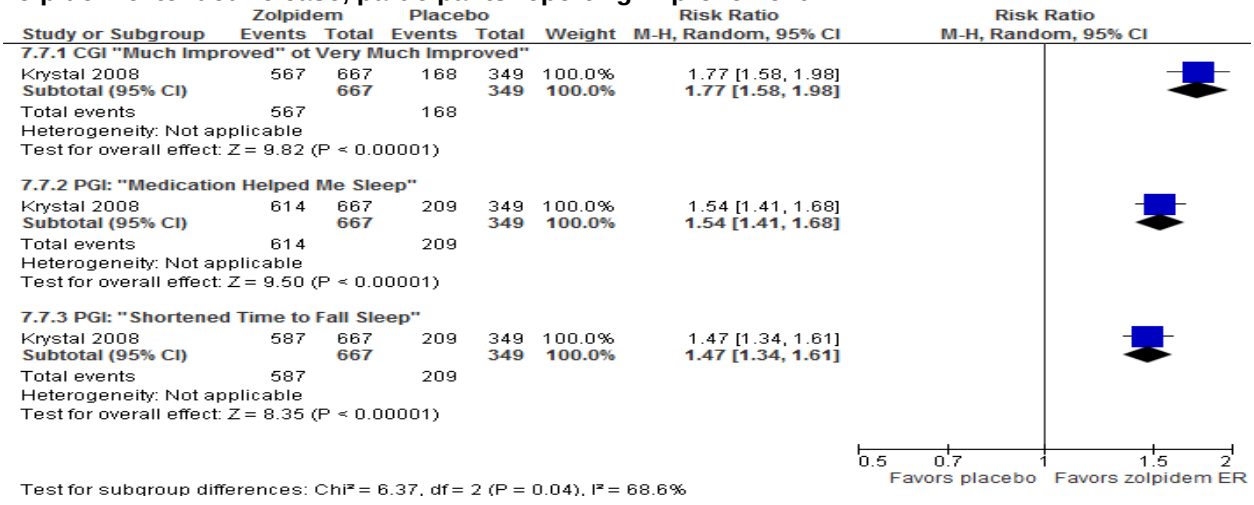
Global Outcomes

Clinician-rated CGI outcome, "much or very much improvement," favored zolpidem extended release over placebo (85 percent vs. 48 percent) (low strength of evidence).

Sleep Outcomes

Improvements in sleep onset latency, total sleep time, and wake time after sleep onset were greater in the zolpidem extended release group compared with the placebo group. Strength of evidence was insufficient for all outcomes. Zolpidem extended release led to greater improvements in Patient's Global Impression (PGI) items compared with placebo (Figure 35) (insufficient evidence).[107] More than 90 percent of participants randomized to zolpidem extended release reported "medication helped me sleep" compared to 60 percent of the participants randomized to placebo (insufficient evidence).

Figure 35. Clinical global impression and patient's global impression items at week 24 for zolpidem extended release, participants reporting improvement



Secondary Outcomes

Krystal et al. reported that the Epworth Sleepiness Scale was significantly lower in the zolpidem extended release group compared with the placebo group during the double-blind treatment phase.[107] At month 5, mean change from baseline was -2.5 and -1.8 points in the zolpidem extended release and placebo groups, respectively (p=0.02).

Adverse Effects

Withdrawals for any reason were greater with placebo than zolpidem extended release (48 percent vs. 36 percent).[107] Conversely, withdrawals due to adverse effects were greater with zolpidem extended release than placebo (8 percent vs. 5 percent). Reports of at least one adverse effect were also greater with zolpidem extended release than placebo (63 percent vs. 51 percent). Strength of evidence was low for all outcomes. No rebound insomnia was reported over the first 3 nights following discontinuation of zolpidem extended release.

Efficacy of Nonbenzodiazepine Hypnotics in Older Adults

Eszopiclone

Overview

We identified one randomized, double-blind, placebo-controlled trial evaluating eszolpiclone that enrolled older adults (Table 15).[108] The trial randomized 388 participants with a mean age of 72; 63 percent were women. Most participants were white. Participants randomized to eszopiclone received a 2 mg dose. The duration of the study was 12 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

Table 15. Overview and strength of evidence: efficacy of nonbenzodiazepine hypnotics in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Eszopiclone 2 mg vs. placebo *(1 RCT; N=388)*					
Global Outcomes					
Remission from Insomnia disorder based on ISI	1 (386)	37 (71/193)	24 (47/193)	Favors eszopiclone RR= 1.51 [1.11 to 2.06] ARR= 0.13 [0.3 to 0.22] NNT= 8	Low (moderate study limitations and unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes, *mean change from baseline*	1 (382)	-	-	NS	Low (moderate study limitations, imprecise and unknown consistency)
Total sleep time, self-report, minutes, *mean change from baseline*	1 (382)	-	-	Favors eszopiclone MD= 30.0 [19.7 to 40.3]	Low (moderate study limitations and unknown consistency)
Wake time after sleep onset, self-report, minutes, *mean change from baseline*	1 (380)	-	-	Favors eszopiclone MD= -21.6 [-29.6 to -13.6]	Low (moderate study limitations and unknown consistency)
Sleep quality	1 (388)	-	-	Favors eszopiclone SMD= 0.24 [0.04 to 0.44]	Low (moderate study limitations and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (388)	24 (47/194)	24 (46/194)	NS	Low (moderate study limitations, imprecise and unknown consistency)
Withdrawals due to adverse effects	1 (388)	7 (14/194)	5 (9/194)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Participants with ≥1 adverse effect	1 (388)	59 (115/194)	51 (98/194)	NS	Low (moderate study limitations, imprecise and unknown consistency)
Zolpidem 5 mg vs. placebo (1 RCT; N=166)					
Global Outcomes					

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Not reported					Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes, *mean change from baseline*	1 (152)	-	-	Favors zolpidem MD= -18.3 [-31.2 to -5.4]	Insufficient (moderate study limitations and unknown consistency)
Total sleep time, self-report, minutes, *mean change from baseline*	1 (152)	-	-	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (166)	7 (6/82)	12 (10/84)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Withdrawals due to adverse effects	1 (166)	2 (2/82)	7 (6/84)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Participants with ≥1 adverse effect	1 (166)	63 (52/82)	56 (47/84)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)

ARR=absolute risk reduction; CI=confidence intervals; ND=No statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

Global Outcomes

Low-strength evidence shows that compared with placebo, eszopiclone more often resulted in remission or no clinically significant insomnia, indicated by an ISI score <7 at endpoint (37 percent vs. 24 percent) (Figure 36. The mean difference in mean change from baseline in ISI scores over 12 weeks of was -2.3 points but this difference did not reach our minimum important difference of 7 points, indicating 'responder' to treatment (Table 37).

Figure 36. Efficacy of eszopiclone in older adults: remitters

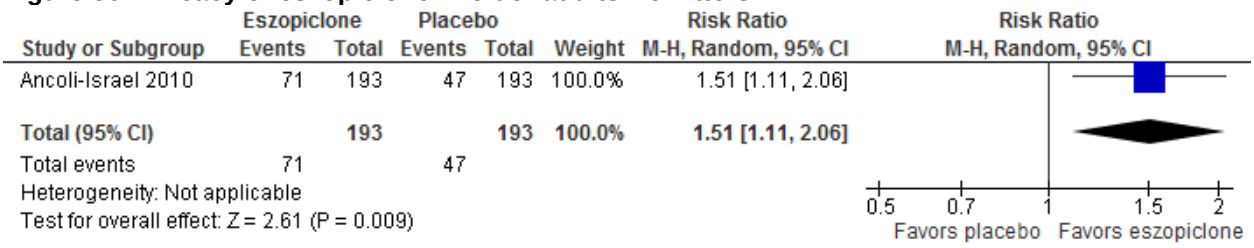
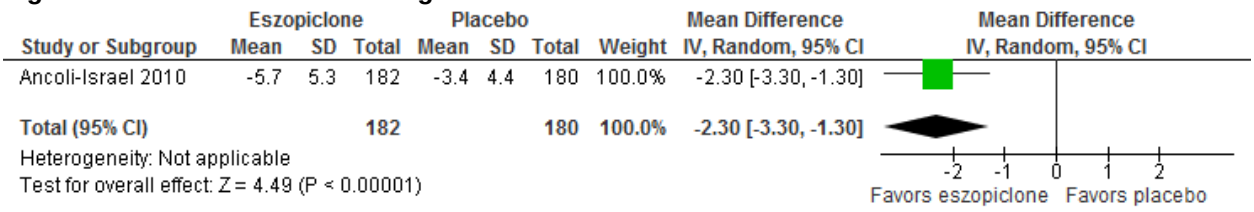


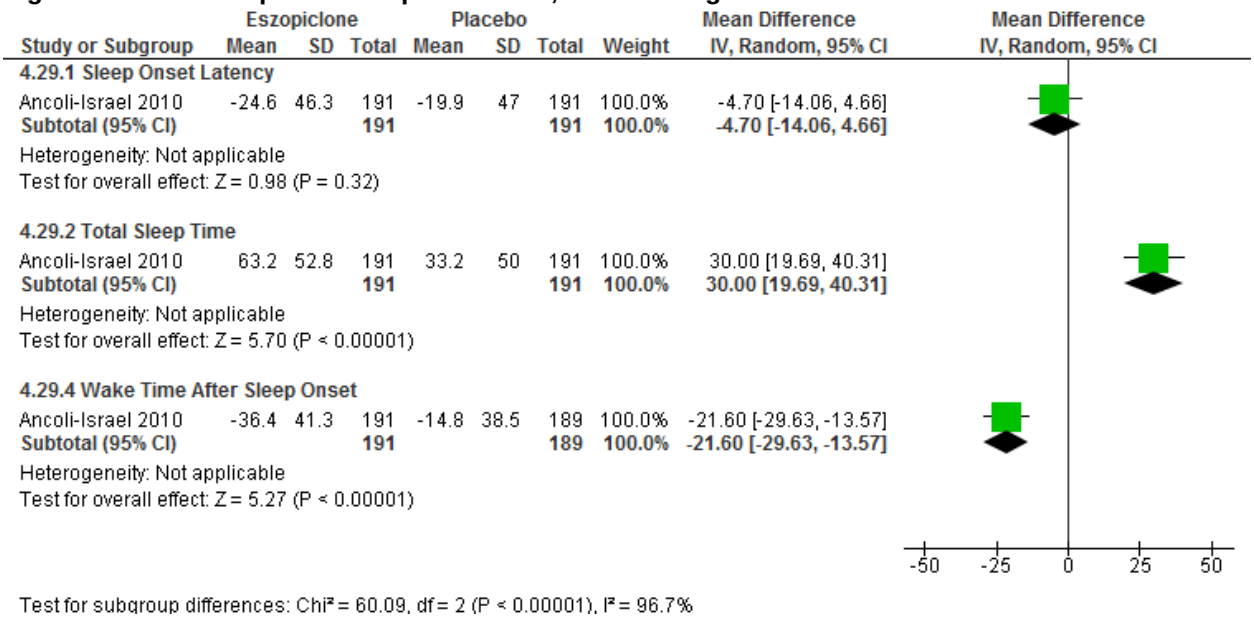
Figure 37. ISI scores: mean change from baseline over 12 weeks



Sleep Outcomes

Subjective sleep onset latency was not improved with eszopiclone versus placebo in older adults. Compared with placebo, improvements were reported for total sleep time and wake time after sleep onset (Figure 38). Over 12 weeks, differences in the mean changes from baseline were 30 minutes for total sleep time and -22 minutes for wake time after sleep onset. Significant improvement in sleep quality was also observed. Strength of evidence for was low for all sleep outcomes.

Figure 38. Patient-reported sleep outcomes, mean changes from baseline



Secondary Outcomes

Quality of life was evaluated with the 36-Item Short-Form Health Survey (SF-36). Compared to placebo, statistically significant improvements were observed in the vitality and general health scales at week 12.

Adverse Effects

There were no statistically significant differences in study withdrawals, participants reporting at least one adverse effect (low strength of evidence), and study withdrawals due to adverse effects (insufficient strength of evidence), between the eszopiclone and placebo groups. The specific adverse effects associated with eszopiclone use was unpleasant taste (12 percent vs. 2 percent in the placebo arm). Based on continued improvements in sleep outcomes in the eszopiclone group during the discontinuation phase, no evidence of rebound effect was reported.

Zolpidem

Overview

We identified one randomized, double-blind, placebo-controlled trial evaluating zolpidem that enrolled older adults.[109] The study was a four-arm trial that also included triazolam and temazepam. The trial randomized 166 participants between the ages of 59 and 85 years. Sex and race were not reported. Participants randomized to zolpidem received a 5 mg dose. The duration

of the study was 4 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

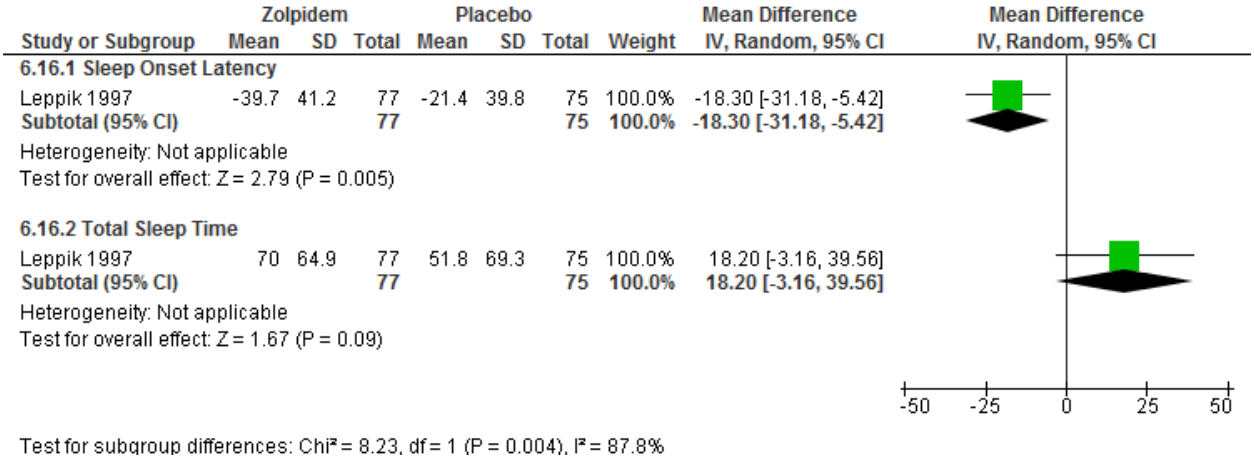
Global Outcomes

Leppik et al. did not report a global outcome.[109]

Sleep Outcomes

Subjective sleep onset latency was improved with zolpidem versus placebo in older adults (low-strength evidence) (Figure 39). Mean decreases from baseline were 40 and 21 minutes for the zolpiem and placebo groups, respectively. Total sleep time was not improved with zolpidem (insufficient evidence).

Figure 39. Efficacy of zolpidem in older adults: patient-reported sleep outcomes, mean changes from baseline



Secondary Outcomes

Leppik 1997 et al. did not report secondary outcomes.[109]

Adverse Effects

There were no statistically significant differences in study withdrawals, study withdrawals due to adverse effects, and participants reporting at least one adverse effect between the zolpidem and placebo groups (insufficient evidence). No specific adverse effect was greater with zolpidem compared with placebo. One participant in the placebo group died during the trial.

Efficacy of Melatonin and Ramelteon in the General Adult Population

Melatonin

Overview of Studies

We identified one RCT that compared melatonin 2 mg prolonged release to placebo reported in two publications (Table 16).[110,111] Initially, the 791 randomized participants were randomized to melatonin or placebo for a 3-week, double-blind, period. After the 3 weeks, the melatonin group remained on melatonin while those in the placebo group were re-randomized to melatonin

or placebo for a 26-week extension period (a total of 711 participants [534 melatonin and 177 placebo]). Our review focuses on the outcomes evaluated during the 26-week extension period. Demographic data for the 711 participants entering the extension period were not provided. However, among the 722 participants completing the initial 3-week period, mean age was 62 years, 69 percent were women, and nearly all were white (99 percent). The trial was conducted in Scotland, reported industry sponsorship, and had a moderate risk of bias.

Table 16. Overview and strength of evidence: efficacy and comparative effectiveness of melatonin and melatonin agonists

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Melatonin prolonged release vs. placebo ***1 RCT; N=711)***					
Global outcomes					
PSQI global score	1 (700)	-	-	MD= -0.39 [-0.71 to -0.08]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (700)	-	-	MD= -6 [-10 to -2.1]	Low (moderate study limitations, and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (711)	21 (113/534)	24 (43/177)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Withdrawals due to adverse effects	1 (711)	5 (26/534)	6 (10/177)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Participants with ≥1 adverse effect	1 (711)	74 (394/534)	77 (136/177)	NS	Low (moderate study limitations and unknown consistency)
Ramelteon vs. placebo ***(5 RCTs; N=3124)***					
Global outcomes					
Not reported					Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	5 (2972)	-	-	NS	Low (moderate study limitations, imprecise, inconsistent)
Total sleep time, self-report, minutes	5 (2781)	-	-	NS	Low (moderate study limitations, imprecise, inconsistent)
Wake time after sleep onset, self-report, minutes	2 (721)	-	-	NS	Low (moderate study limitations, imprecise)
Sleep quality	5 (2973)	-	-	Favors Ramelteon SMD= -0.08 [-0.16 to -0.01]	Low (moderate study limitations, imprecise, inconsistent)
Adverse Effects					
Overall withdrawals	2 (1594)	12 (116/987)	10 (62/607)	Greater with Ramelteon RR= 1.47 [1.11 to 1.94] AR= 0.05 [-0.02 to 0.12]	Low (moderate study limitations and imprecise)
Withdrawals due to adverse effects	3 (1999)	2 (29/1261)	2 (15/738)	NS	Low (moderate study limitations and imprecise)
Participants with ≥1 adverse effect	3 (1999)	46 (579/1262)	46 (336/737)	NS	Moderate (moderate study limitations)

CI=confidence intervals; MD=mean difference; NS=No statistically significant difference; RR=risk ratio; SMD=standardized mean difference

Global Outcomes

Evidence was insufficient regarding melatonin improving global outcomes. The mean difference in PSQI scores between groups was statistically significant but very small (-0.39 points [95% CI, -0.71 to -0.08]).

Sleep Outcomes

Low-strength evidence found melatonin prolonged release improved subjective sleep onset latency. The mean difference between groups was statistically significant but small (6 minutes [95%CI 2 to 10]. Other sleep outcomes were not reported.

Secondary Outcomes

Overall, melatonin prolonged release improved WHO-5 quality of life scores compared with placebo. The mean difference between groups was 0.46 points (95% CI, 0.11 to 0.81).

Adverse Effects

Study withdrawals for any reason (21 percent vs. 24 percent placebo), withdrawals due to adverse effects (5 percent vs. 6 percent), and the proportion of participants reporting at least one adverse effect (74 percent vs. 77 percent) were similar with melatonin prolonged release and placebo. Strength of evidence was insufficient for withdrawals due to adverse effects, and low for the others. There were 15 serious adverse effects in the melatonin prolonged release group and nine in the placebo group (including one death). There were no differences in type or frequency of adverse effects.

Ramelteon (Brand Name Rozerem)

Overview of Studies

We identified five RCTs that met our inclusion criteria, (Table 16.[112-115] Two of the trials, NCT00237497 and NCT00671567 only had results published in a systematic review. The trials randomized 3124 participants; mean age was 45; 63 percent were women. In the two trials that reported race/ethnicity, most participants were white. Two trials were conducted in the United States,[112,115] one in Japan,[114] and two were multinational.[112,113] Dosing ranged from 4 to 16 mg. All trials were short term (4 – 5 weeks) with the exception of Mayer et al., which lasted 6 months.[113] All trials reported industry sponsorship and had moderate risk of bias.

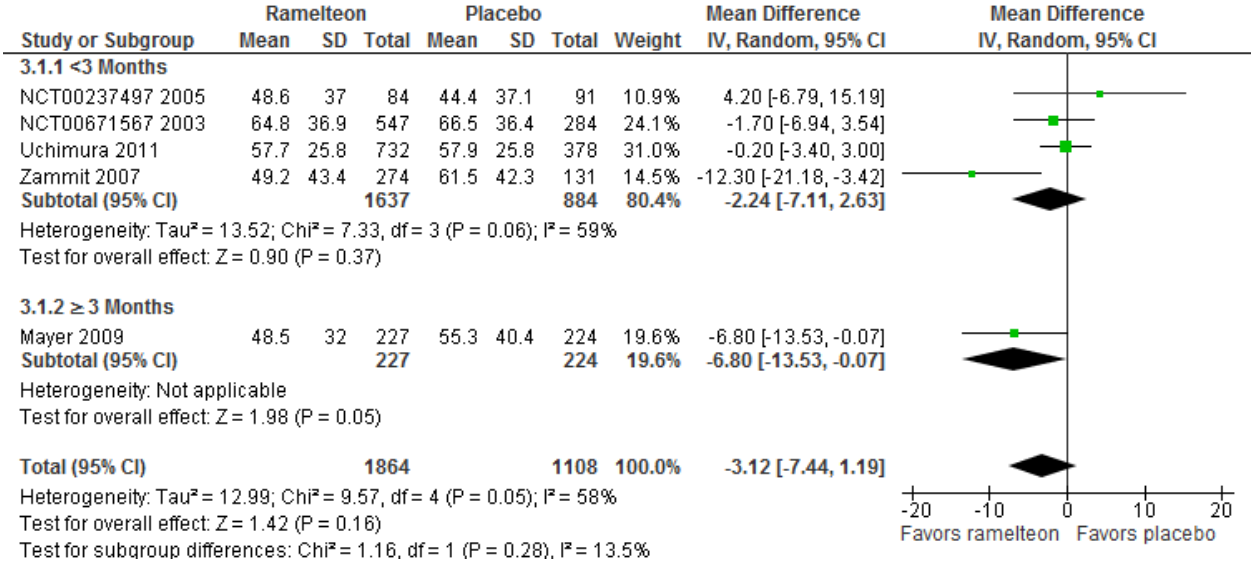
Global Outcomes

None of the ramelteon trials reported global outcomes.

Sleep Outcomes

Patient-reported sleep outcomes from the five trials meeting eligibility criteria are presented in Figure 40. Ramelteon did not reduce sleep onset latency compared with placebo (low-strength evidence). The only study longer than 3 months[113] reported an improvement in sleep onset latency of -6.8 minutes (95% CI, -13.5 to -0.1).[113]

Figure 40. Efficacy of ramelteon: subjective sleep latency, minutes



Low-strength evidence found that ramelteon did not significantly improve total sleep time or wake time after sleep onset compared to placebo. Ramelteon statistically improved sleep quality compared with placebo, but the effect was less than small (ES 0.08), indicating little difference between groups (moderate-strength evidence). The six-month trial by Mayer et al., the only trial lasting more than 3 months, reported no difference between treatment groups on any sleep outcome.[113]

Secondary Outcomes

Secondary outcomes were not reported.

Adverse Effects

Not all trials reported adverse effects. Ramelteon resulted in more withdrawals than placebo (12 percent vs. 10 percent; p=0.007; k=2; low strength evidence). Ramelteon and placebo were similar in withdrawals due to adverse effects (2 percent vs. 2 percent) and participants having at least one adverse event (46 percent vs. 46 percent) (strength of evidence was low and moderate, respectively). No specific adverse effect was greater with ramelteon than with placebo. Neither trial reported evidence of tolerance or withdrawal symptoms. No randomized studies evaluated long-term effects (1 year or longer) of ramelteon.

Efficacy of Melatonin and Ramelteon in Older Adults

Overview

We identified one randomized, double-blind, placebo-controlled trial evaluating ramelteon that enrolled older adults (Table 17). [116] Additional outcomes data for this trial was obtained from the systematic review by Kuriyama et al.[112] The three-arm trial randomized 829 participants with a mean age of 72; 59 percent were women. Race was not reported. Participants were randomized to 4 or 8 mg dose. Study duration was 5 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

Table 17. Overview and strength of evidence: efficacy of melatonin agonists in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Ramelteon vs. placebo, older adults ***(1 RCT; N=829)***					
Global outcomes					
Not reported					Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (826)	-	-	Favors Ramelteon MD= -10.1 [-15.6 to -4.6]	Low (moderate study limitations, and unknown consistency)
Total sleep time, self-report, minutes	1 (825)	-	-	NS	Low (moderate study limitations imprecise, and unknown consistency)
Wake time after sleep onset, self-report, minutes	0				Insufficient
Sleep quality	1 (826)	-	-	NS	Low (moderate study limitations and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (829)	15 (82/555)	17 (46/274)	NS	Low (moderate study limitations, imprecise and unknown consistency)
Withdrawals due to adverse effects	1 (829)	3 (15/555)	3 (8/274)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Participants with ≥1 adverse effect	1 (829)	56 (313/555)	51 (141/274)	NS	Low (moderate study limitations, imprecise and unknown consistency)

CI=confidence intervals; MD=mean difference; NS=No statistically significant difference

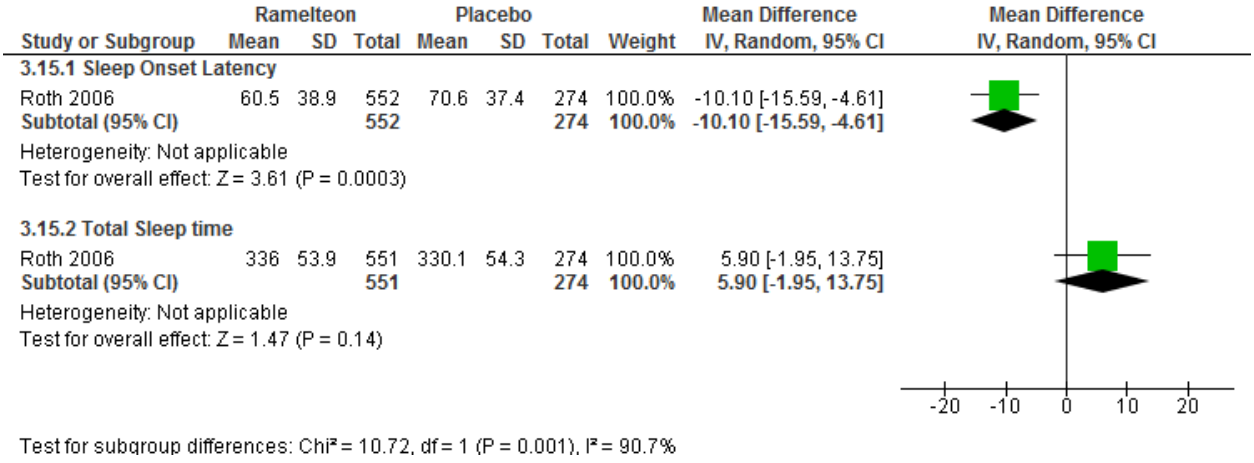
Global Outcomes

A global impression inventory was completed by both participants and clinicians. No statistically significant differences between treatment groups were reported (data was not reported).

Sleep Outcomes

Patient-reported sleep outcomes from all included trials are presented in Figure 41. Ramelteon dosage arms were combined for analyses (Figure 41).[112] Ramelteon reduced sleep onset latency by 10 minutes compared with placebo. Ramelteon did not improve total sleep time or sleep quality over the 5 week study duration. Strength of evidence for all outcomes was low.

Figure 41. Efficacy of ramelteon in older adults: subjective sleep latency and total sleep time, minutes



Secondary Outcomes

Roth et al. did not report secondary outcomes.

Adverse Effects

We found no statistically significant differences in study withdrawals, study withdrawals due to adverse effects, or participants reporting at least one adverse effect between the ramelteon and placebo groups. Strength of evidence was insufficient for study withdrawals due to adverse effects, low for the others. No specific adverse effect was greater with ramelteon compared to placebo.

Efficacy of Benzodiazepine Hypnotics in the General Adult Population

Overview of Studies

We identified three eligible RCTs[117-119] that assessed the efficacy of benzodiazepines in the general adult population. Wu et al[119] compared temazepam with placebo; Mitler et al.[117] compared triazolam and flurazepam with placebo; and Minnekeer et al.[118] compared quazepam with placebo.(Table 18).

Table 18. Overview and strength of evidence: efficacy and comparative effectiveness of the benzodiazepine hypnotics in general adult populations

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence
Temazepam vs. placebo 1 RCT; n=39					
Global Outcomes					
Not reported	0				Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (34)			Favors temazepam MD= -30.9 [-50.43 to -11.4]	Insufficient (moderate study limitations, and unknown

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence
					consistency)
Total sleep time, self-report, minutes	1 (34)			Favors temazepam MD= 93.5 [47.6 to 139.4]	Insufficient (moderate study limitations, and unknown consistency)
Sleep efficiency, percent	1 (34)			Favors temazepam MD= 14.1 [5.8 to 22.4]	Insufficient (moderate study limitations, and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (39)	15 (3/20)	10.5 2/19)	NS	Insufficient
Withdrawals due to adverse effects	1 (39)	15 (3/20)	0 (0/19)	NS	Insufficient
Triazolam vs placebo 1 RCTs; n=14					
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (14)			NA	Insufficient
Total sleep time, self-report, minutes	1 (14)			NA	Insufficient
Adverse Effects					
NR					Insufficient
Flurazepam vs. placebo 1 RCT; N=14					
Global Outcomes					
Not reported	0				Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (14)			NA	Insufficient
Total sleep time, self-report, minutes	1 (14)			NA [b]	Insufficient
Quazepam vs. placebo (1 RCT; N=108)					
Sleep Outcomes					
Sleep onset latency, self-report [c]	1 (108)			NS[c]	Insufficient
Total sleep time, self-report	1 (108)			Favors quazepam, based on scale	Insufficient
Adverse Effects					
Overall withdrawals	1 (152)	25 (25/101)	37 (19/51)	Favors Quazepam RR 0.34 [0.23 to 0.50]	Insufficient (high study limitations, and unknown consistency)
Withdrawals due to adverse effects	1 (152)	5 (5/101)	6 (3/51)	NS	Insufficient

CI=confidence interval; MD=mean difference; NS=no significant difference

Efficacy of Temazepam in the General Adult Populations

Overview of Studies

One RCT[119] met our inclusion criteria and compared temazepam to placebo in the general adult population. Wu et al. randomized participants to cognitive behavioral therapy alone, temazepam alone, cognitive behavioral therapy with temazepam, or placebo drug alone. For this aspect of the review we examined only the temazepam and placebo arms. Demographic information was not reported for the temazepam and placebo arms separately, but among the four treatment arms, the mean age was 38 years and 53 percent were women. Temazepam recipients initially received 7.5 mg nightly with gradual increases up to 30 mg, and then a decrease to 15 mg in the last treatment week for a total of 8 weeks. The trial was conducted in China and had government funding. Wu et al.[119] had moderate risk of bias.

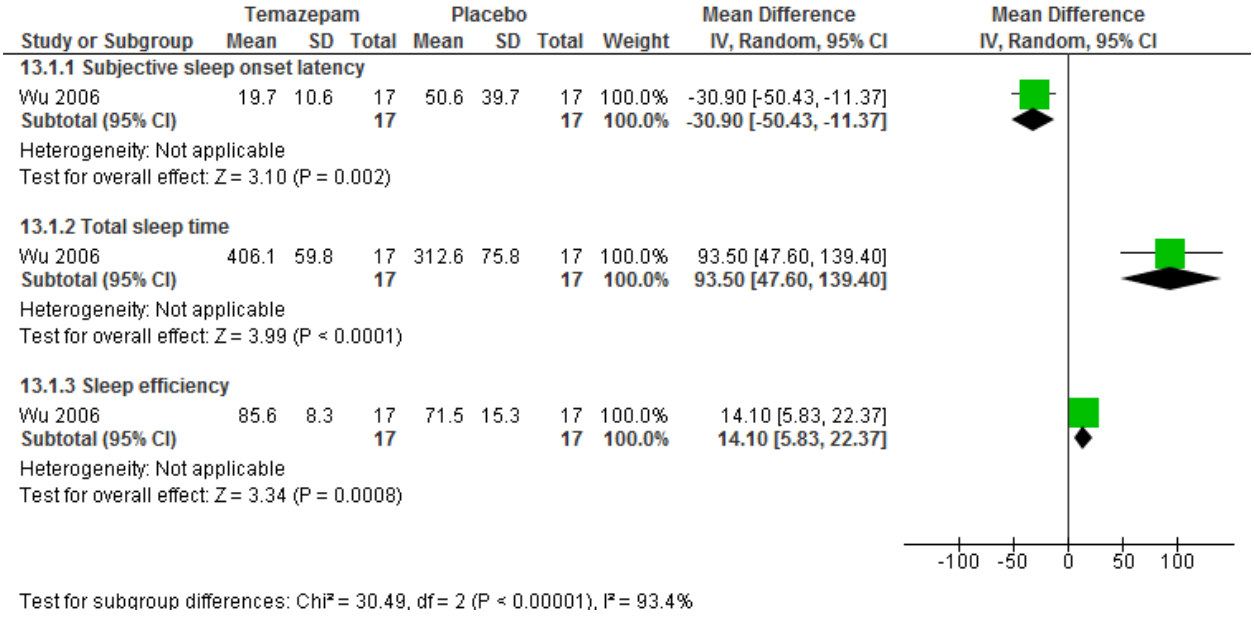
Global Outcomes

Wu et al.[119] did not report global outcomes.

Sleep Outcomes

Sleep outcomes are presented in Figure 42. Temazepam reduced SOL by 31 minutes, increased TST by 94 minutes, and improved sleep efficiency by 14 percentage points compared with placebo. Evidence was insufficient for both outcomes.

Figure 42. Efficacy of temazepam: sleep latency minutes, total sleep time minutes, and sleep efficiency (percent)



Secondary Outcomes

Temazepam significantly reduced the daytime dysfunction component of the PSQI compared with placebo.

Adverse Effects

There were no significant differences in overall withdrawals or withdrawals due to adverse effects between temazepam and placebo. Specific adverse effects were not reported. Strength of evidence was insufficient.

Efficacy of Triazolam in the General Adult Population

Overview of Studies

We identified one RCT[117] that met our inclusion criteria and compared triazolam to placebo among the general adult population. Mitler et al.[117] randomized participants to triazolam 0.5 mg, flurazepam 30 mg, or placebo; comparisons between the triazolam (n=7) and placebo (n=7) arms are discussed here. The mean age was 41 years; 79 percent were women; race was not reported. The trial lasted 5 weeks and was conducted in the United States; funding was not reported. The trial had a high risk of bias.

Global Outcomes

Mitler et al.[117] did not report any global outcomes.

Sleep Outcomes

Mitler et al.[117] reported sleep onset latency and total sleep time but did not report between-group comparisons and did not report outcomes in such a way that between-group comparisons could be calculated.

Secondary Outcomes

Mitler et al.[117] found no significant between-group differences in the Multiple Sleep Latency test or the Target Pursuit Test.

Adverse Effects

Mitler et al.[117] did not report overall withdrawals, withdrawals due to adverse effects, or specific adverse effects.

Efficacy of Flurazepam in General Adult Populations

Overview of Studies

We identified one RCT[117] that met our inclusion criteria and compared flurazepam to placebo among the general adult population. Mitler et al.[117] randomized participants to triazolam 0.5 mg, flurazepam 30 mg, or placebo. Comparisons between the flurazepam (n=7) and placebo (n=7) arms are discussed here. The mean age was 41 years; 79 percent were women; race was not reported. The trial lasted 5 weeks and was conducted in the United States; funding was not reported. The trial had a moderate risk of bias.

Global Outcomes

Mitler et al.[117] did not report any global outcomes.

Sleep Outcomes

Mitler et al.[117] reported sleep onset latency and total sleep time but did not report between-group comparisons and did not report outcomes in such a way that between-group comparisons could be calculated. Strength of evidence was insufficient.

Secondary Outcomes

Mitler et al.[117] found no significant between-group differences in the Multiple Sleep Latency test or the Target Pursuit Test.

Adverse Effects

Mitler et al.[117] did not report overall withdrawals, withdrawals due to adverse effects, or specific adverse effects. Strength of evidence was insufficient.

Efficacy of Quazepam in General Adult Populations

Overview of Studies

We identified one RCT[118] that met our inclusion criteria and compared quazepam to placebo among the general adult population. Minnekeer et al.[118] randomized participants to quazepam 15 mg, flunitrazepam 2 mg, or placebo. However, since flunitrazepam is not approved by the FDA and is not legally available in the United States, results from only the flurazepam and placebo arms are discussed here. The mean age was 54 years; 63 percent were women; race was not reported. The trial lasted 4 weeks and was conducted in Belgium and the Netherlands. The trial did not report funding and had high risk of bias.

Global Outcomes

Minnekeer et al.[118] did not report any global outcomes.

Sleep Outcomes

Using nonstandard scales, Minnekeer et al.[118] found that flurazepam significantly improved total sleep time compared with placebo, but had no significant effect on sleep onset latency. Strength of evidence was insufficient.

Secondary Outcomes

Minnekeer et al.[118] found no significant differences in number of awakenings or in a nonstandard global sleep score at the end of treatment.

Adverse Effects

There were no significant differences between quazepam and placebo groups in the proportion of participants withdrawing for any reason or withdrawing due to adverse effects. Strength of evidence was low for withdrawals and insufficient for the others. The most common adverse effect for both groups was daytime somnolence.

Efficacy of Benzodiazepine Hypnotics in Older Adults

We identified two RCTs[54,120] that met our inclusion criteria and assessed the efficacy and adverse effects of benzodiazepines in older adults (Table 19). Morin et al.[62] compared temazepam with placebo; Reeves et al.[120] compared triazolam and flurazepam with placebo.

Table 19. Overview and strength of evidence: efficacy of the benzodiazepine hypnotics in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence
Temazepam vs. placebo **1 RCT; n=40**					
Sleep Outcomes					
Total sleep time, self-report, minutes	1 (35)			NS	Insufficient
Wake time after sleep onset, self-report, minutes	1 (35)			Favors temazepam MD= -22.3 [-36.8 to -7.7]	Insufficient (moderate study limitations, and unknown consistency)
Sleep efficiency, percent	1 (35)			Favors temazepam MD= 9.2 [2.8 to 15.6]	Insufficient (moderate study limitations, and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (40)	10 (2/20)	15 (3/20)	NS	Insufficient
Withdrawals due to adverse effects	1 (40)	15 (3/20)	0 (0/20)	NS	Insufficient
Triazolam vs. placebo **1 RCTs; n=23**					
Sleep Outcomes					
Sleep onset latency, self-report *Based on score where 0=slower than usual, 1=same as usual, 2=faster than usual*	1 (23)			Favors triazolam	Insufficient
Total sleep time, self-report *Based on score where 0=less than 5 hours, 1=5 to 6 hours, 2=6.1 to 7 hours, 3=7.1 to 8 hours, and 4=more than 8 hours*	1 (23)			Favors triazolam	Insufficient
Sleep quality *Based on scale where 1=lightly, 2=moderate, 3=deeply*	1 (23)			Favors triazolam	Insufficient
Adverse Effects					
Overall withdrawals	1 (28)	21 (3/14)	14 (2/14)	NS	Insufficient
Withdrawals due to adverse effects	1 (28)	0 (0/14)	7 (1/14)	NS	Insufficient
Participants with ≥1 adverse effect	1 (28)	57 8/14	29 4/14	NS	Insufficient
Flurazepam vs. placebo **1 RCT; N=24**					
Sleep Outcomes					
Sleep onset latency, self-report *Based on score where 0=slower than usual, 1=same as usual, 2=faster*	1 (24)			Favors flurazepam	Insufficient

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence
than usual					
Total sleep time, self-report *Based on score where 0=less than 5 hours, 1=5 to 6 hours, 2=6.1 to 7 hours, 3=7.1 to 8 hours, and 4=more than 8 hours*	1 (24)			NS	Insufficient
Sleep quality *Based on scale where 1=lightly, 2=moderate, 3=deeply*	1 (24)			Favors flurazepam	Insufficient
Adverse Effects					
Overall withdrawals	1 (27)	8 (1/13)	14 (2/14)	NS	Insufficient
Withdrawals due to adverse effects	1 (27)	0 (0/13)	7 (1/14)	NS	Insufficient
Participants with ≥1 adverse effects	1 (27)	46 6/13	29 4/14	NS	Insufficient

CI=confidence interval; ISI=Insomnia Severity Index; MD=mean difference; min=minutes; NS=no significant difference; PSQI=Pittsburgh Sleep Quality Index

Efficacy of Temazepam in Older Adults

We identified one RCT[62] that met our inclusion criteria and compared temazepam with placebo among older adults. Morin et al.[62] et al. randomized participants to cognitive behavioral therapy alone, temazepam alone, cognitive behavioral therapy with temazepam, or placebo drug alone. For this aspect of the review, we examined only the temazepam and placebo arms. Morin et al.[62] included only adults at least 55 year old; the 40 participants randomized had a mean age of 65 years and 60 percent were women; Morin et al.[62] did not report other baseline characteristics. Morin et al. randomized participants to temazepam 7.5 mg nightly, with increases up to 30 mg nightly possible, depending on response and adverse effects; or to placebo drug. The trial lasted 8 weeks, was conducted in the United States, and had government sponsorship. Morin et al.[62] had low risk of bias.

Global Outcomes

Morin et al.[62] did not report any global outcomes.

Sleep Outcomes

Morin et al.[62] found that wake time after sleep onset and sleep efficiency were significantly better with temazepam than placebo (insufficient evidence), but there was no significant difference in total sleep time (insufficient evidence).

Secondary Outcomes

Morin et al.[62] found no significant difference in the Sleep Impairment Index with temazepam compared with placebo (insufficient evidence).

Adverse Effects

There was no significant difference between temazepam and placebo groups in the proportion of participants withdrawing for any reason or withdrawing due to adverse effects.

Efficacy of Triazolam in Older Adults

We identified one RCT[120] that met our inclusion criteria and compared triazolam with placebo among older adults. Reeves et al.[120] randomized participants to triazolam, flurazepam, or placebo. For this aspect of the review, we examined only the triazolam and placebo arms. Reeves et al.[120] included only adults at least 61 year old; the 28 participants randomized to triazolam or placebo had a mean age of 70 years and 68 percent were women; Reeves et al.[120] did not report other baseline characteristics. Reeves et al. randomized participants to triazolam 0.25 mg nightly or to placebo drug. The trial lasted four weeks and was conducted in the United States; funding was not reported. Reeves et al.[120] had moderate risk of bias.

Global Outcomes

Reeves et al.[120] did not report any global outcomes.

Sleep Outcomes

Using nonstandard scales, Reeves et al.[120] found that sleep onset latency, total sleep time, and sleep quality were significantly better with triazolam than placebo. Strength of evidence for all outcomes was insufficient.

Secondary Outcomes

Reeves et al.[120] found that triazolam significantly improved the sense that medication helped sleep and feeling rested in the morning but had no significant difference in having dreams compared with placebo.

Adverse Effects

There were no significant differences between triazolam and placebo groups in the proportion of participants withdrawing for any reason, withdrawing due to adverse effects, or having at least one adverse effect. The most common adverse effect was daytime drowsiness. Strength of evidence was insufficient.

Efficacy of Flurazepam in Older Adults

Reeves et al.[120] randomized participants to triazolam, flurazepam, or placebo. For this aspect of the review, we examined only the flurazepam and placebo arms. Reeves et al.[120] included only adults at least 61 year old; the 27 participants randomized to flurazepam or placebo had a mean age of 70 years and 59 percent were women; Reeves et al.[120] did not report other baseline characteristics. Reeves et al. randomized participants to flurazepam 15 mg nightly or to placebo drug. The trial lasted 4 weeks and was conducted in the United States; funding was not reported. Reeves et al.[120] had moderate risk of bias.

Global Outcomes

Reeves et al.[120] did not report any global outcomes.

Sleep Outcomes

Using nonstandard scales, Reeves et al.[120] found that sleep onset latency and sleep quality were significantly better with flurazepam than placebo, but there was no significant difference in total sleep time. Strength of evidence for all outcomes was insufficient.

Secondary Outcomes

Reeves et al.[120] found that flurazepam had no significant difference in the sense that medication helped sleep, feeling rested in the morning, or having dreams compared with placebo.

Adverse Effects

There were no significant differences between flurazepam and placebo groups in the proportion of participants withdrawing for any reason, withdrawing due to adverse effects, or having at least one adverse effect. The most common adverse effect was daytime drowsiness. Strength of evidence was insufficient.

Efficacy of Antidepressants in the General Adult Population

Overview of Studies

We identified two RCTs that compared doxepin to placebo in the general adult population[121,122] (Table 20). Hajak et al.[121] randomized 47 participants to doxepin 25 mg (increasing to 50 mg of doxepin as needed) or placebo. Krystal et al. [122] randomized 229 participants to either doxepin 3 mg, doxepin 6 mg, or placebo. Because different doses of doxepin were used, efficacy outcomes could not be pooled.

Both trials had active treatment lasting four weeks. Overall, the mean age was 45 and 74 percent were women. Only Krystal et al. 2011[122] reported ethnicity: in that trial, 48 percent of participants were white. Hajak et al.[121] was conducted in Germany and Krystal et al. [122] was conducted in the United States. Both RCTs reported industry sponsorship. Both trials had moderate risk of bias.

Table 20. Efficacy of doxepin in the general adult population

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Doxepin vs. placebo, nonelderly 2 RCTs; n analyzed=261					
Global Outcomes					
Global improvement, *based on Clinical Global Impression Scale*	1 (40)			Favors doxepin MD -0.58 [-1.05 to -0.12]	Insufficient (moderate study limitations, unknown consistency)
Sleep Outcomes					
Total sleep time, self-report, minutes	1 (221)			Favors doxepin 3 mg MD 11.9 (CI NR) Favors doxepin 6 mg MD 17.3 (CI NR)	Insufficient (moderate study limitations, unknown consistency)
Wake time after sleep onset, self-report, minutes	1 (221)			Favors doxepin 3 mg MD −10.2 (CI NR). Favors doxepin 6 mg MD −14.2 (CI NR)	Insufficient (moderate risk of bias, unknown consistency)
Sleep quality	1 (40)			Favors doxepin	Insufficient (moderate study limitations, unknown consistency)
Adverse Effects					
Overall withdrawals	2 (276)	12 (21/177)	12 (12/99)	NS	Insufficient (moderate study limitations,

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
					imprecise, and unknown consistency)
Withdrawals due to adverse effects	2 (276)	4 (7/177)	4 (4/99)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Participants with ≥1 adverse effect	1(268)	42 (73/172)	43 (41/96)	NS	Low (moderate study limitations, imprecise, and unknown consistency)

CI=confidence interval; MD=mean difference; NSD=no significant difference; RR=relative risk; SD=standard deviation; SE=standard error

Global Outcomes

Hajak et al.[121] found doxepin significantly enhanced global improvement on the Clinical Global Impression Scale compared with placebo (2.42 vs. 3.00, where lower scores indicate more improvement) (low strength of evidence). Hajak et al. found no significant differences between treatment groups in severity of illness from the Clinical Global Impression Scale.

Sleep Outcomes

Krystal et al.[122] found that both doxepin doses significantly improved total sleep onset and wake time after sleep onset compared to placebo (Table 20). Strength of evidence was low for both outcomes. Hajak et al.[121] found that doxepin 25 mg significantly improved sleep quality compared with placebo (52 vs. 41 on a 100-point visual-analog scale).

Secondary Outcomes

Krystal et al. [122] found no significant differences between the doxepin dose groups and placebo in the Digit Symbol Substitution Test, the Symbol Copying Test, or daytime sleepiness at 4 weeks. Hajak et al. found doxepin 25 mg significantly improved energy and working ability compared with placebo.

Adverse Effects

There were no significant differences in overall study withdrawals, study withdrawals due to adverse effects, participants reporting at least one adverse effect, daytime, or headache between participants receiving doxepin versus placebo.

Efficacy of Antidepressants in Older Adults

Overview of Studies

We identified two RCTs[123,124] that compared doxepin to placebo in older adults (Table 21). Krystal et al.[123] randomized 240 participants to either doxepin 1 mg, doxepin 3 mg, or placebo. Lankford et al.[124] randomized 254 participants to doxepin 6 mg or placebo. Because different doses of doxepin were used, efficacy outcomes could not be pooled. Krystal et al.[123] had an active treatment duration of 12 weeks and Lankford et al.[124] was 4 weeks. The mean age was 72,

65 percent were women, and 84 percent were white. Both RCTs were conducted in the United States and reported industry sponsorship. Both trials had low risk of bias.

Table 21. Efficacy of doxepin in older adults

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Doxepin vs. placebo 2 RCTs; n=494					
Global Outcomes					
ISI *mean score at endpoint*	1 (240)			Favors doxepin 1 mg MD -2.1 [-3.6 to -0.6] Favors doxepin 3 mg MD -2.4 [-3.9 to -0.9]	Low
ISI, *mean score at endpoint*	1 (254)			Favors doxepin 6 mg MD -1.5 [-2.9 to -0.1]	
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (240)			Favors doxepin 1 mg MD -18.0 [-28.0 to -8.0] Favors doxepin 3 mg MD -15.6 [-26.4 to -4.8]	Low (unknown consistency)
Total sleep time, self-report, minutes	1 (240)			Favors doxepin 1 mg MD 45.5 [23.9 to 67.1] Favors doxepin 3 mg MD 63.4 [41.2 to 85.6]	Insufficient (imprecise, inconsistenct)
Total sleep time, self-report, minutes	1 (254)			NS (6 mg dose)	
Wake time after sleep onset, self-report, minutes	1 (254)			NS (6 mg dose)	Insufficient (imprecise, and unknown consistency)
Sleep efficiency	0				Insufficient
Sleep quality *scale from -3 to 3 (-3 = extremely poor and 3 = excellent)*	1 (240)			Favors doxepin 1 mg SMD 0.36 [0.05 to 0.67] Favors doxepin 3 mg SMD 0.56 [0.25 to 0.88]	Insufficient (imprecise, and unknown consistency)
Sleep Quality *scale from -3 to 3 (-3 = extremely poor and 3 = excellent)*	1 (254)			NS (6 mg dose)	
Adverse Effects					
Overall withdrawals	2 (495)	7 (21/289)	11 22/206)	NS	Low (imprecise, and unknown consistency)
Withdrawals due to adverse events	2 (495)	2 (5/289)	2 (4/206)	NS	Insufficient (imprecise, and unknown consistency)
Participants with ≥1 adverse events	2 (495)	32 (93/289)	34 69/205)	NS	Low (imprecise, and unknown consistency)

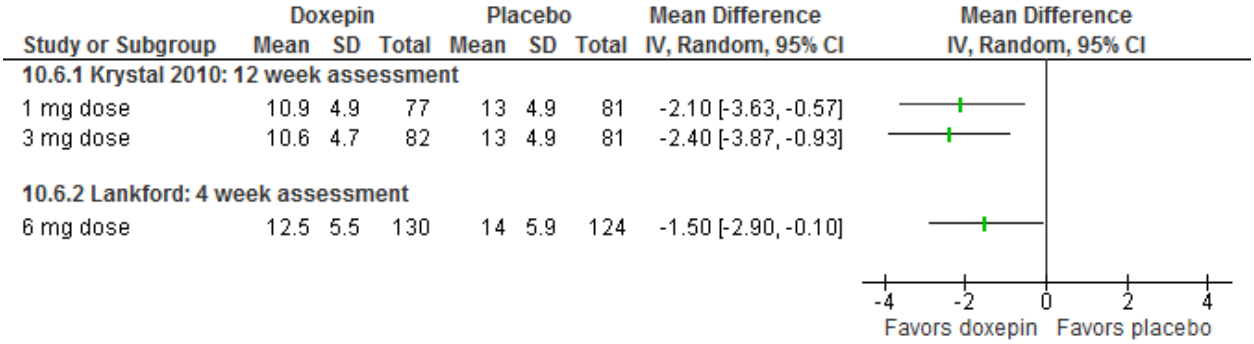
CGI=Clinical Global Impression; CI=confidence interval; ISI=Insomnia Severity Index; NSD=no significant difference; RR=relative risk

Global Outcomes

Both trials reported ISI scores, but because different doses of doxepin were used, outcomes could not be pooled. Our analyses found ISI scores were significantly improved with doxepin 1 and 3 mg doses compared with placebo at 12 weeks (Figure 43) Lankford et al. 2012[124] also

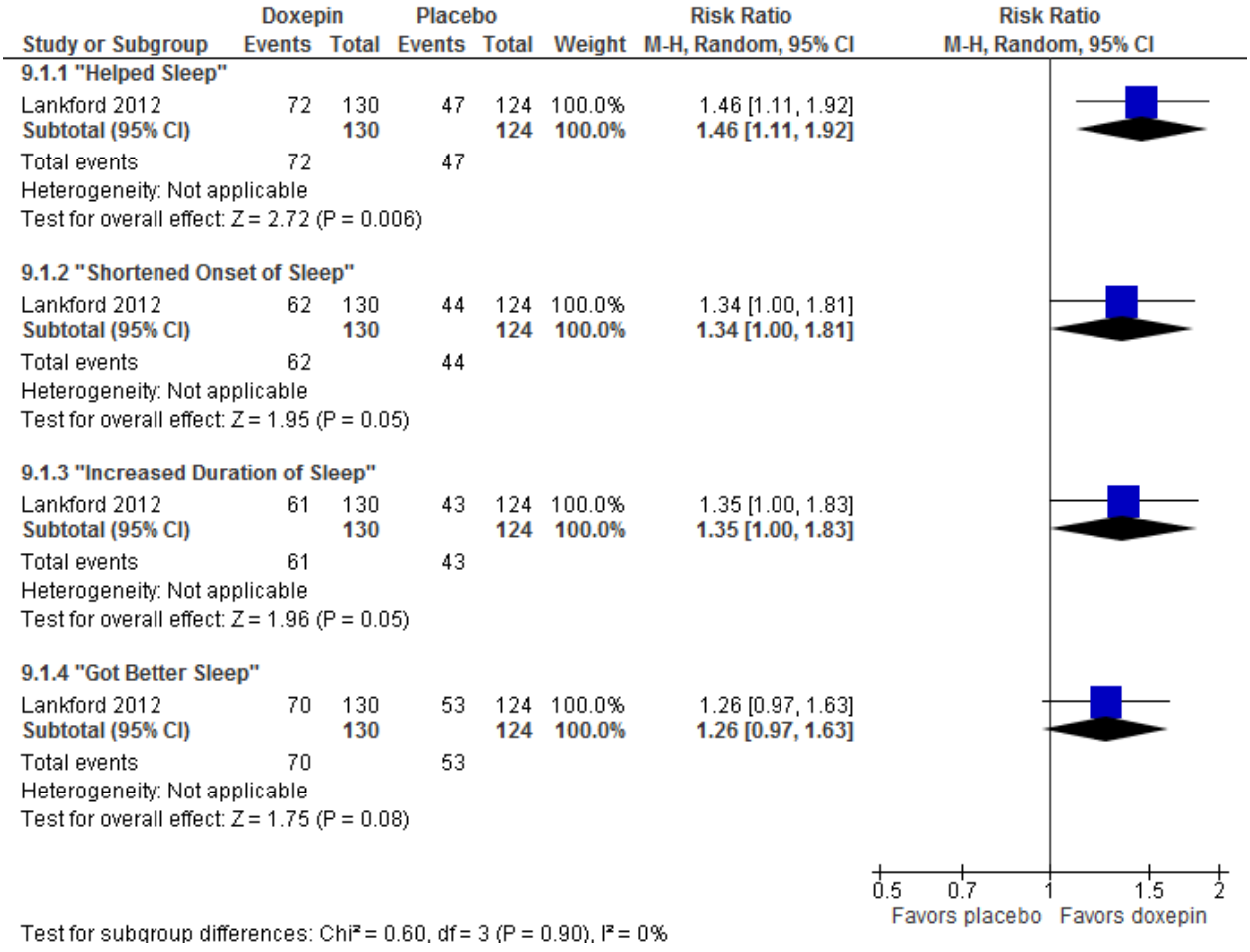
found small but significant improvement in ISI scores with doxepin 6 mg compared with placebo at 4 weeks. Strength of evidence was low.

Figure 43. Efficacy of doxepin in older adult population: ISI scores



Lankford et al.[124] found that doxepin 6 mg significantly improved three of four sleep components of the PGI scale compared with placebo at 4 weeks (Figure 44). Lankford et al.[124] found CGI scores were not significantly different with doxepin 6 mg compared with placebo at 4 weeks. Krystal et al. 2010[123] found that CGI scores were significantly better with doxepin 1 mg or doxepin 3 mg versus placebo at 12 weeks

Figure 44. Lankford: patient global impression of sleep quality at final visit, participants reporting improvement



Sleep Outcomes

Krystal et al.[123] reported significant improvements in sleep onset latency (Figure 45), total sleep time (Figure 46), and sleep quality (Figure 48) with doxepin 1 and 3 mg doses compared with placebo after 12 weeks of therapy. Strength of evidence was low. At 4 weeks, Lankford et al.[124] reported that doxepin 6 mg improved total sleep time, wake time after sleep onset (Figure 47), or sleep quality compared with placebo based on their analysis of covariance methods. Our analyses found that doxepin 6 mg did not improve these sleep outcomes compared with placebo (insufficient strength of evidence). At 12 weeks, Krystal et al. 2010[108] found all five sleep quality components of the PGI scale were significantly better with doxepin 1 mg and doxepin 3 mg compared with placebo. Lankford et al.[124] also found that doxepin 6 mg significantly improved three of four sleep components of the PGI scale compared with placebo at 4 weeks.

Figure 45. Efficacy of doxepin in older adult populations: sleep onset latency

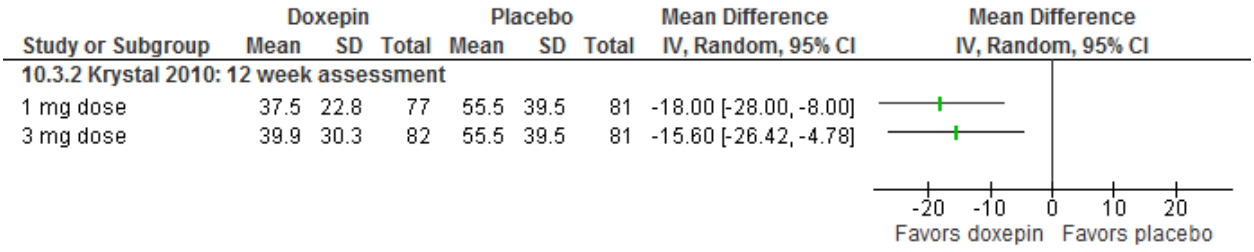


Figure 46. Efficacy of doxepin in older adult population: total sleep time

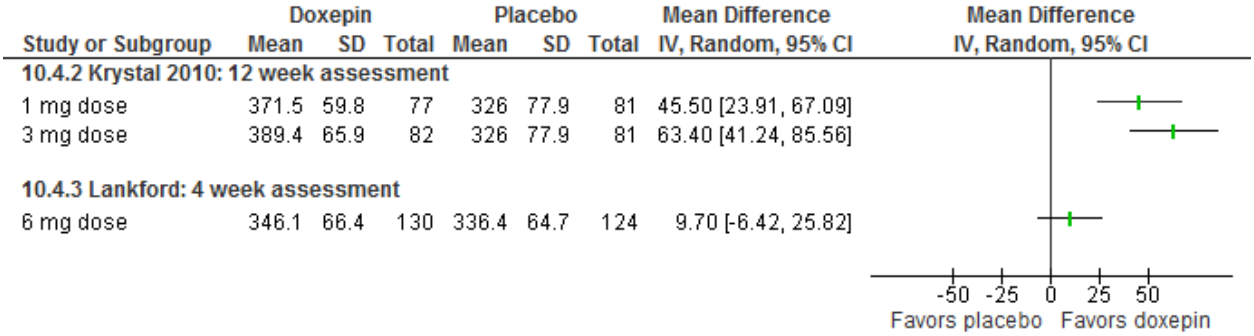


Figure 47. Efficacy of doxepin in older adult populations: wake time after sleep onset

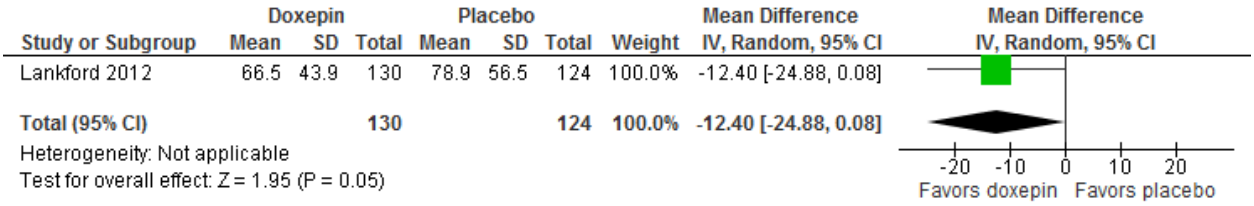
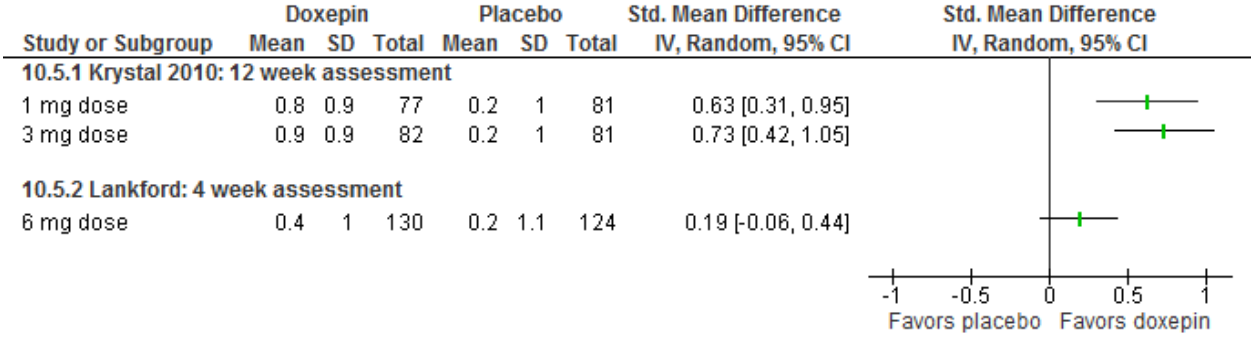


Figure 48. Efficacy of doxepin in older adult populations: sleep quality



Krystal et al. 2010[123] found no significant differences in next-day residual function and effects between both doxepin doses and placebo in the Digit Symbol Substitution Test, the Symbol Copying Test, or daytime sleepiness at 12 weeks.

Adverse Effects

There were no significant differences in overall study withdrawals, study withdrawals due to adverse effects, participants reporting at least one adverse, or daytime somnolence, between participants receiving doxepin versus placebo. However, there were significantly fewer headaches (RR 0.29 [95% CI 0.29 to 0.70]) among participants receiving doxepin versus placebo.

Efficacy of Trazodone

Overview of Study

We identified one relevant RCT[125] that compared trazodone with CBT to CBT alone (Table 22). The study by Zavesicka et al.[125] lasted 8 weeks and was conducted in the Czech Republic. Among the 20 participants randomized, the mean age was 47 and 75 percent were women; ethnicity was not reported. Participants were randomized to trazodone controlled release 150 mg 30 minutes before bedtime with weekly CBT sessions versus weekly CBT sessions alone. The RCT had government sponsorship.

Table 22. Efficacy of trazodone in the general adult population: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N))	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Trazodone with CBT vs. CBT 1 RCT; n=20					
Global Outcomes					
ISI	1 (20)			NS	Insufficient
Sleep Outcomes					
NR					Insufficient
Adverse Effects					
Overall withdrawals	1 (20)	0 (0/10)	0 (0/10)	NS	Insufficient
Withdrawals due to adverse effects	1 (20)	0 (0/10)	0 (0/10)	NS	Insufficient
Participants with ≥1 adverse effect	0				Insufficient

CBT=cognitive behavioral therapy; CI=confidence interval; ISI=Insomnia Severity Index; MD=mean difference; NS=no significant difference

Global Outcomes

Zavesicka et al.[125] reported the ISI and found no significant difference between trazodone with CBT versus CBT alone (11.0 vs. 10.1, respectively) (insufficient evidence). However, both treatment groups had significant improvements from baseline.

Sleep Outcomes

Zavesicka et al.[125] did not report sleep outcomes.

Secondary Outcomes

Zavesicka et al.[125] reported the Epworth Sleepiness Scale (ESS) score and found no significant difference between trazodone with CBT vs. CBT alone (8.1 vs 9.2) (insufficient evidence). However, both treatment groups had significant improvements from baseline.

Adverse Effects

In the Zavesika et al. RCT,[125] no patient withdrew due to adverse effects. Adverse effects were not otherwise reported.

Comparative Effectiveness of Pharmacologic interventions for Insomnia Disorder

Comparative Effectiveness of Zolpidem versus Temazepam

Overview of Study

We identified one RCT that compared the nonbenzodiazepine zolpidem 10 mg to benzodiazepine temazepam 20 mg over a 4 week treatment period (Table 23).[126] Among the 223 randomized, baseline characteristics were available for 159 participants; mean age was 46 years; 67 percent were women. The trial was conducted in the Netherlands, reported industry sponsorship, and had a moderate risk of bias.

Table 23. Overview and strength of evidence: comparative effectiveness of nonbenzodiazepines versus benzodiazepines

Comparison Outcome Measure	# Trials (n)	Treatment A % (n/N)	Treatment B % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 10 mg vs. Temazapam 20 mg ***1 RCT; N=223)***					
Global Outcomes					
CGI, much-very much improved	1 (157)	21.6 (16/74)	32.5 (27/83)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (159)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Total sleep time, self-report, minutes	1 (159)			Favors zolpidem MD= 27.0 [2.1 to 51.9]	Insufficient (moderate study limitations and unknown consistency)
Wake time after sleep onset, self-report, minutes	1 (159)			NS	Insufficient (moderate risk of bias, imprecise, and unknown consistency)
Adverse Effects					
Overall withdrawals	0				Insufficient
Withdrawals due to adverse effects	0				Insufficient
Participants with ≥1 adverse effect	0				Insufficient

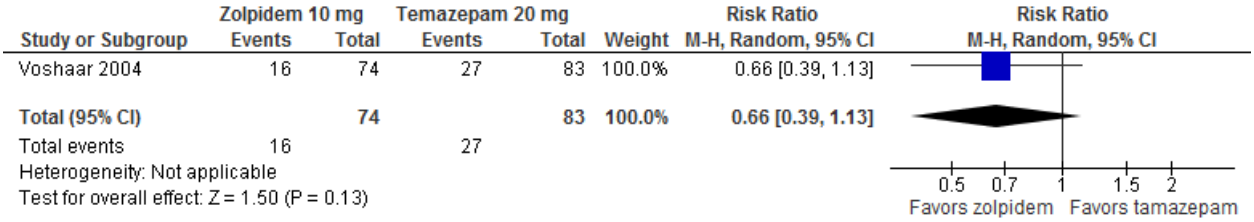
CI=confidence intervals; MD=mean difference; NNH=number needed to harm. NNT=number needed to treat; NS=No statistically significant difference; RR=risk ratio; SMD=standardized mean difference

Global Outcomes

Evidence was insufficient to assess differences between groups in global outcomes. following 4 weeks of treatment (Figure 49). Voshaar et al. found that 22 percent in the zolpidem

group and 33 percent in the temazepam group reported that symptons were “much-very much” improved on the CGI.

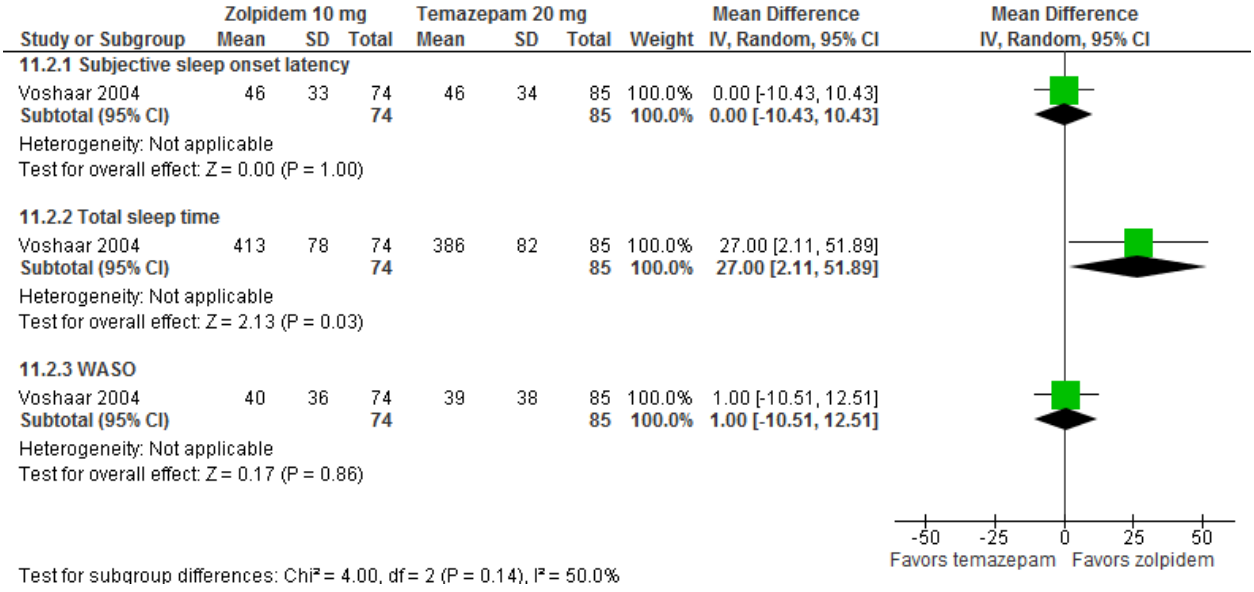
Figure 49. Global improvement of zolpidem versus temazepam, participants reporting improvement



Sleep Outcomes

Sleep outcomes are presented in (Figure 50). Evidence was insufficient to assess sleep outcomes. Voshaar et al. find that total sleep time improved with zolpidem compared with temazapam. There were no differences between groups for sleep onset latency and wake time after sleep onset.

Figure 50. Comparative effectiveness of zolpidem versus tamazepam: subject sleep outcomes



Secondary Outcomes

No secondary outcomes were reported.

Adverse Effects

Overall withdrawals, withdrawals due to adverse effects, and participants with at least one adverse effect were not reported according to treatment arm. Nine participants withdrew due to an adverse effects. No participant experienced a major adverse effects.

Zolpidem Versus Zaleplon

Overview of Studies

We identified two 4-week RCTs evaluating zaleplon versus placebo that also included a zolpidem arm (Table 24).[99,100] Head-to-head comparisons between zaleplon and zolpidem were not provided, which limited our assessment of comparative effectiveness. Among the 965 participants randomized to zaleplon and zolpidem, mean age was 42 years, 62 percent were women, and most were white (91 percent). One trial was conducted in the United States[100] and one was conducted in Canada and Europe.[99] Participants were randomized to zaleplon 5, 10, or 20 mg doses and zolpidem 10 mg. Both trials reported industry sponsorship and had moderate risk of bias.

Table 24. Overview and strength of evidence: efficacy and comparative effectiveness of nonbenzodiazepines

Comparison Outcome Measure	# Trials (n)	Treatment A % (n/N)	Treatment B % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zaleplon 5-20 mg vs. Zolpidem 10 mg ***2 RCTs; N=965)***					
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (301)			Favors zolpidem 10 mg dose versus zaleplon 5 mg dose MD= -13.7 [-25.1 to -2.3] NS zolpidem 10 mg versus zaleplon 10 mg	Insufficient (moderate study limitations, imprecise, and unknown consistency)
Total sleep time, self-report, minutes	2 (965)	-	-	No direct comparison and reported data does not allow analysis	Insufficient
Wake time after sleep onset, self-report, minutes	0				Insufficient
Sleep efficiency	0				Insufficient
Sleep Quality, *Improved sleep quality, self-report*	2 (870)	57 (376/656)	64 (137/214)	NS	Moderate (moderate study limitations)
Adverse Effects					
Overall withdrawals	2 (965)	12 (85/726)	12 (28/239)	NS	Low (moderate study limitations and imprecise)
Withdrawals due to adverse effects	2 (958)	4 (29/720)	6 (14/238)	NS	Low (moderate study limitations and imprecise)
Participants with ≥1 adverse effect	2 (958)	7 (510/720)	7 (175/238)	NS	Moderate (moderate study limitations)

CI=confidence intervals; MD=mean difference; NS=no statistically significant difference

Global Outcomes

The included trials did not report global outcomes.

Sleep Outcomes

Sleep outcomes from included trials are presented in Table 24, and Figures 51 and 52. Zolpidem 10 mg improved sleep onset latency compared to zaleplon 5 mg by approximately 14 minutes.[100] Improvements in sleep onset latency were similar between the zolpidem and zaleplon

10 mg dose groups (insufficient evidence). We could not evaluate the comparative effectiveness of the two nonbenzodiazepine agents for total sleep time from the data reported (insufficient evidence). Both trials reported that zaleplon and zolpidem did not consistently improve median total sleep time compared with placebo over the 4 week study durations.

Sleep quality with zaleplon was similar to zolpidem at week 4 (57 percent vs. 64 percent) (moderate strength of evidence). There were also no significant differences between the individual zaleplon doses versus zolpidem at week 4.

Figure 51: Comparative effectiveness of zaleplon versus zolpidem: sleep onset latency

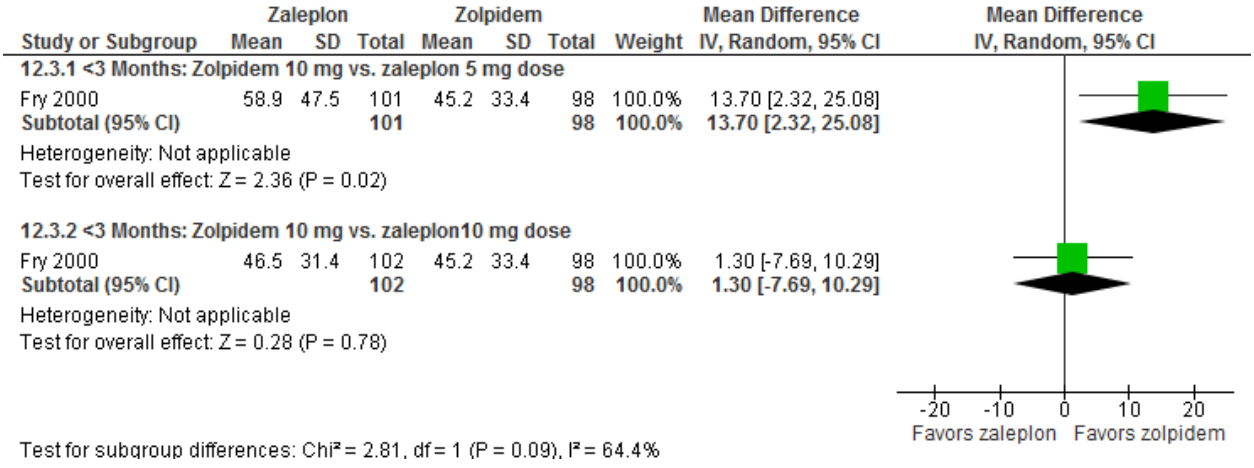
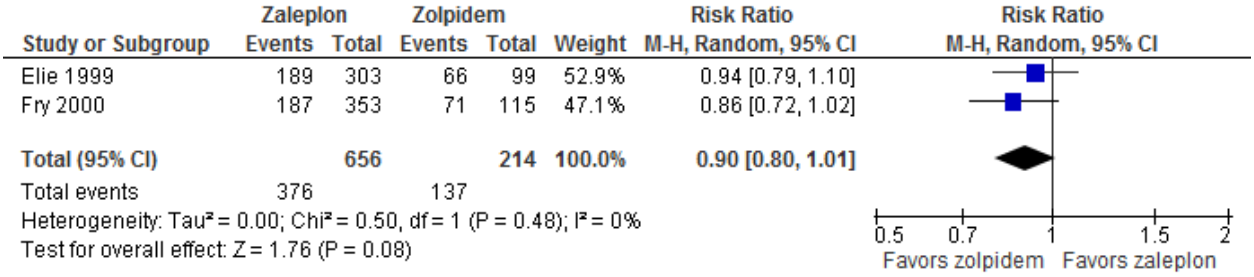


Figure 52: Comparative effectiveness of zaleplon versus zolpidem: sleep quality, participants reporting improvement



Secondary Outcomes

No secondary outcomes were reported in the included trials.

Adverse Effects

Adverse effects were reported in both trials. There were no differences in withdrawals for any reason (12 percent each) and the proportion of participants reporting at least one adverse event (7 percent each) between the zaleplon and zolpidem groups. Withdrawals due to adverse effects were comparable between groups. Incidences of withdrawal symptoms and rebound insomnia following discontinuation were reported for zolpidem. Neither trial reported evidence of tolerance or withdrawal symptoms associated with zaleplon use.

Efficacy of Various Complementary and Alternative Medicine Treatments

Efficacy and Comparative Effectiveness of Complementary and Alternative Interventions

Key Points

- A previous high quality systematic review found insufficient evidence on the efficacy of acupuncture as a treatment alone or as an adjunctive treatment. Updating results from this review, we conclude that the evidence remains insufficient to draw conclusions about the efficacy of acupuncture used alone or as an adjunctive treatment improves global outcomes.

Efficacy of Acupuncture

Overview of Included Studies

We identified one relevant systematic review addressing efficacy of acupuncture for insomnia disorder that was of sufficient quality to include in lieu of de novo extraction (Table 25). Cheuk et al.[23] searched databases through October 2012, had no language restrictions, distinguished different types of acupuncture, and included 33 primary studies. Twenty one of 33 trials included trials involved treatments lasting 4 or more weeks.

We identified two RCTs assessing the efficacy of acupuncture for insomnia that were not included in the previous systematic review (Table 26).[127] Hatchel et al. randomized participants to acupuncture or sham acupuncture and had moderate risk of bias; the study was underpowered but could be pooled with one comparison in the previous systematic review. Acupuncture versus sham acupuncture was included in the Cheuk et al. review. Hatchel et al. can be used to update this analysis for one outcome that was included in the review and the recently published trial. We also identified one trial that assessed acupuncture as an adjunct therapy. Adjunctive acupuncture versus other treatment alone was compared in Cheuk et al. Huo et al.[128] randomized participants to acupuncture using meridian and Anmian acupoints or to acupuncture using only meridian acupoints, had moderate risk of bias, and can be used to update the Cheuk et al. analysis for one outcome.

Hachul et al.[127] was conducted in Brazil, enrolled only women, randomized 18 participants, and had a study duration of 5 weeks.[127] Huo et al., a 4-week study, was conducted in China.[128]

Table 25. Efficacy of acupuncture: description and conclusions from previous systematic review

Study Information	Literature Through; SR Quality	Population; Relevant Comparison	Author Conclusion Strength of Evidence
Cheuk, 2012[23] Cochrane Depression, Anxiety and Neurosis Group) 33 trials (all high risk of bias) Only 17 trials provided relevant outcomes data	Literature search through October 2012 Good	Individuals clinically diagnosed with insomnia using standardized criteria Any type of acupuncture versus a passive control (no treatment, placebo; sham acupuncture)	"Due to poor methodological quality, high levels of heterogeneity and publication bias, the current evidence is not sufficiently rigorous to support or refute acupuncture for treating insomnia. Larger high-quality clinical trials are required." Insufficient

Table 26. Efficacy of acupuncture in the general adult population: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Intervention % (n/N) or Mean (SD)	Control % (n/N) or Mean (SD)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Acupuncture vs. sham acupuncture 1 SR; 8 RCT; n=364					
Global Outcomes					
PSQI	8 (364)			WMD: -2.11 [-3.24 ti -0.98]	Insufficient (high study limitations)
Sleep Outcomes					
NR					Insufficient
Adverse Effects					
Total adverse events	1 (32)	6.3% (1/16)	0% (0/16)	OR: 3.19 [0.12 to 84.43]	Insufficient (high study limitations)
Adjunctive acupuncture vs. single treatment 1 SR; 4 RCT; N=206					
Global outcomes					
PSQI	4 (206)			WMD: -2.50 [-3.20 ti -1.80]	Insufficient (high study limitations)
Sleep Outcomes					
Adverse Effects					
Total adverse effects	1 (45)	0% 0/23	27% (6/22)	OR: 0.05 [0.00 to 1.03]	Insufficient (high study limitations)

CI=confidence interval; PSQI=Pittsburgh Sleep Quality Index; SD=standard deviation; SE=standard error; WMD=weighted mean difference

Global Outcomes

Cheuk et al.,[23] Hachul et al.,[127] and Huo et al.[128] reported PSQI scores. In the trial of acupuncture versus sham acupuncture, Hachul et al.[127] found no significant differences in PSQI scores and no significant change from baseline in either group. In contrast, in the trial of acupuncture at meridian and Anmian acupoints versus at meridian acupoints alone, Huo et al.[128] found significantly better (lower) PSQI scores with acupuncture at meridian and Anmian acupoints (5.49 vs. 7.77), but no significant improvements from baseline within either group. Updating the Cheuk et al. review strengthens the evidence for these two comparisons (Figures 53

and 54). However, because all the trials in that review were rated high risk of bias, we maintain that this evidence is insufficient.

Figure 53. Efficacy of acupuncture in the general adult population: PSQI score

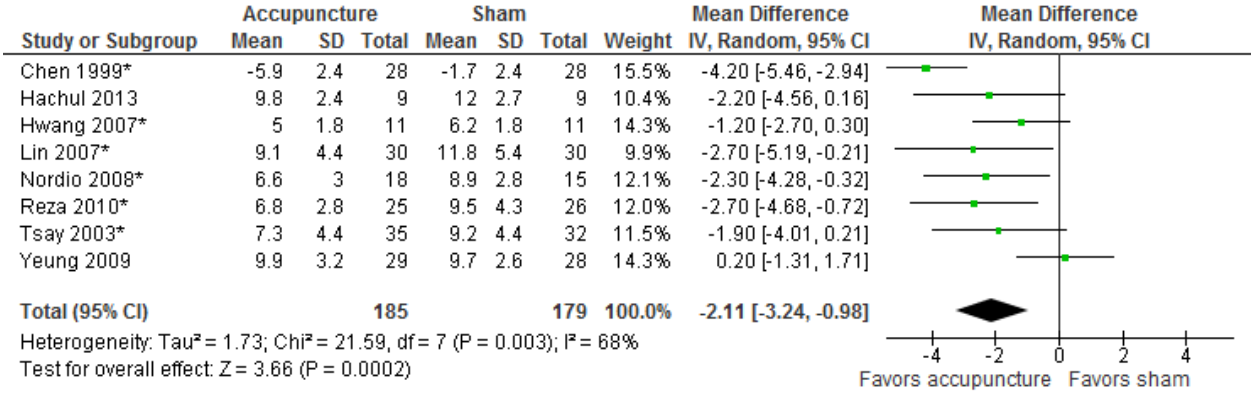
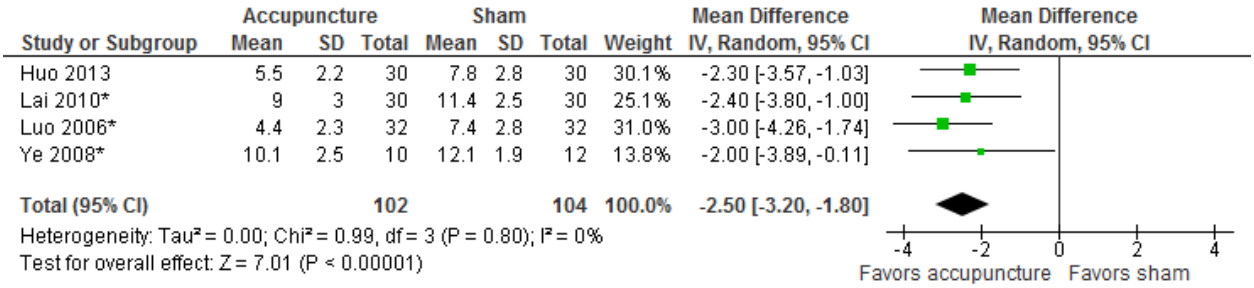


Figure 54. Efficacy of adjunctive acupuncture in the general adult population: PSQI score



Sleep Outcomes

Neither of the studies published since Cheuk et al. reported sleep outcomes; therefore, we could not update those outcomes.

Secondary Outcomes

In their trial of acupuncture versus sham acupuncture, Hachul et al.[127] reported the Beck Depression Inventory but found no significant difference between groups in scores (33.28 vs. 32.5) and no significant improvement from baseline within either group. Hachul et al.[127] also reported the World Health Organization Quality of Life score. They found no significant difference between treatment groups in any component, and significant improvement from baseline for only the psychological component within the acupuncture group. In their trial of acupuncture at meridian and Anmian acupoints versus meridian acupoints alone, Huo et al.[128] found significantly better therapeutic efficacy and lower self-rating depression scores (25.53 vs. 30.80) but not self-rating anxiety scores (31.23 vs. 32.00) for meridian and Anmian acupoints. Self-rating depression scores and self-rating anxiety scores improved significantly from baseline within both groups. Huo et al.[128] also found significantly better treatment efficacy in the meridian plus Anmian acupuncture group.

Adverse Effects

Fewer than half of the studies included in Cheuk et al. reported adverse effects, and the adverse effects that were reported were minor. Compared with an intervention used by an RCT in this review, the Cheuk et al. systematic review[23] found no significantly greater risk for adverse effects for needle acupuncture versus placebo or sham acupuncture (OR 3.19 [95% CI, 0.12 to 84.43]) or for needle acupuncture with other treatment versus other treatment alone (OR 0.05 [95% CI, 0.00 to 1.03]).

Huo et al.[128] reported withdrawals by treatment group. No withdrawals occurred in either treatment group. Updating the data from the systematic review provides insufficient evidence to draw conclusions about the rates of adverse effects between groups.

Comparative Effectiveness of Acupuncture Treatments

We identified one RCT that compared acupuncture to another intervention for insomnia. Zhang et al.[129] randomized participants to acupuncture based on brain and mind or to acupuncture based on symptoms and reported a self-rating sleeping scale and found significantly better (lower) scores in the acupuncture mind-body group (21.31 vs. 24.56) and significant improvement from baseline within both groups. Evidence was insufficient to assess the comparative effectivenss between these two types of acupuncture.

Efficacy of Various Complementary and Alternative Medicine Treatments

Overview of Studies

We identified two relevant systematic reviews that examined CAM treatments for insomnia. Cooper et al.[130] and Taibi et al.[131] were assessed as having fair quality and were therefore used in lieu of de novo extraction for those comparisons (Table 27). Cooper et al. identified five RCTs of homeopathy for insomnia, all had high risk of bias; they identified another RCT in an update.[130,132] Only one RCT showed a significant difference in the sleep impairment index with homeopathy compared with placebo. Taibi et al.[131] identified 29 clinical trials and eight open-label studies of valerian for insomnia. Most studies found no significant difference in sleep outcomes between valerian and the control treatment.

We identified five RCTs that met our inclusion criteria and were not included in one of the previous systematic reviews (Table 28). Lin et al.[133] included participants from the general adult population; Harrison et al. included only men; Hachul et al.,[135] Afonso et al.,[136] and Oliveira et al.[136] included only post-menopausal women aged 50 to 65 years; and Abbasi et al.[137] included only adults aged 60 to 75 years.

Each trial studied a different treatment. Lin et al.[133] randomized participants to three Wuling capsules or placebo three times a day for 4 weeks; Harrison et al.[138] randomized men to homeopathic complex or placebo before supper and at bedtime for 4 weeks. All the studies with post-menopausal women lasted 16 weeks: Hachul et al.[135] randomized participants to isoflavone 80 mg or placebo (frequency not reported); and Oliveira et al.[139] randomized participants to therapeutic massage, passive movement, or an unspecified control.

Most RCTs were small. Only Lin et al.[140] had a sample size over 100. Trials lasted from 4 weeks to 4 months. Across the three RCTs reporting participants' age, the mean age was 35. Across all RCTs, 74 percent of participants were women. Race was rarely reported. Harrison et al.[138] was conducted in South Africa; Hachul et al.[135] and Oliveira et al.[139] in Brazil; and the

other RCTs in China.[133] All RCTs reported government sponsorship. Harrison et al.,[138] Hachul et al.,[135] and Oliveira et al.[139] had moderate risk of bias; while Lin et al.[133] had low risk of bias.

Table 27. Efficacy of complementary and alternative medicine treatments: description and conclusions from previous systematic reviews

Study Information	Literature Through; SR Quality	Population; Relevant Comparison	Author Conclusion Strength of Evidence
Cooper, 2010[130,132] Homeopathy k=5 RCTs; n=199 k=8 observational studies: n unclear	Literature search through July 2009 Fair	Individuals with insomnia Homeopathic medicines versus placebo	The evidence available does not demonstrate a statistically significant effect of homeopathic medicines for insomnia treatment. Existing RCTs were of poor quality and were likely to have been underpowered. Insufficient

Taibi, 2007[131]
Valerian
k=29 RCTs;
n=1941
 	
k=8 open label studies;
n=20 to 830 participants
	Search date not reported
	
	Fair
		Individuals with insomnia or sleep disturbance
		
		Valerian or valerian in combination versus mostly a passive control (placebo; other CAM)
			The evidence does not support the clinical efficacy of valerian as a sleep aid for insomnia. Valerian was found to be safe with only rare adverse effects.
			
			Insufficient

Table 28. Efficacy of complementary and alternative medicine treatments: overview and strength of evidence

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Wuling capsule vs. placebo **1 RCT; n=186**					
Global Outcomes					
PSQI	1 (186)	7.53 (3.11)	7.60 (3.20)	NS	Insufficient (imprecise and unknown consistency)
Sleep Outcomes					
Adverse Effects					
Overall withdrawals	1 (212)	13 (14/106)	11 (12/106)	NS	Insufficient (imprecise and unknown consistency)
Withdrawals due to adverse effects	1 (212)	1 (1/106)	0 (0/106)	NS	Insufficient (imprecise and unknown consistency)
Participants with ≥1 adverse effect	1 (106)	10 (9/94)	7 (6/92)	NS	Insufficient (imprecise and unknown consistency)
Homeopathic complex vs. placebo 1 RCT; n=28					
Global Outcomes					
Not reported	0				Insufficient
Sleep Outcomes					
Sleep onset latency, self-report, minutes	1 (28)			Favors homeopathic complex MD -1.3 (CI NR)	Insufficient (moderate study limitations, imprecise

Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
					and unknown consistency)
Adverse Effects					
Overall withdrawals	1 (34)	22 (4/18)	13 (2/16)	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
Isoflavones vs. placebo 1 RCT; n=37					
Global Outcomes					
Not reported					Insufficient
Sleep Outcomes					
Sleep quality *Moderate or intense insomnia on Kupperman Index*	1 (37)			Favors isoflavones	Insufficient (moderate study limitations, imprecise and unknown consistency)
Adverse Effects					
Passive stretching vs. no treatment 1 RCT; N=29					
Global Outcomes					
ISI	1 (29)	11.4 (SE, 1.3)	13.7 (SE, 1.2)	NS	Insufficient
Sleep Outcomes					
Not reported					
Adverse Effects					
Overall withdrawals	1 (37)	33.3 (7/21)	6.3 (1/16)	NS	Insufficient
Withdrawals due to adverse effects	1 (37)	0 (0/21)	0 (0/16)	NS	Insufficient
Participants with ≥ 1 adverse effect	1 (37)	0 (0/21)	0 (0/16)	NS	Insufficient
Therapeutic massage vs. control 1 RCT; n=30					
Global Outcomes					
ISI	1 (30)			Favors therapeutic massage MD 7 p=0.006	Insufficient

CI=confidence interval; MD=mean difference; NS=no significant difference; PSQI=Pittsburgh Sleep Quality Index

Global Outcomes

Evidence was insufficient to draw conclusions about the efficacy of either of the approaches to treating insomnia. Lin et al.[133] found no significant difference between Wuling capsule and placebo in PSQI. However, no significant improvements from baseline in PSQI were found in either treatment group. ISI scores did not differ significantly between passive stretching and the control group.[136] Compared with the control group, ISI scores were significantly better (lower) in the yoga group but not the passive stretching group. Afonso 2012 ISI scores were significantly better (lower) with therapeutic massage than control at 16 weeks, but not at 8 weeks.[139]

Sleep Outcomes

Evidence was insufficient to draw conclusions about the efficacy of either of the approaches to treating insomnia. Harrison et al.[138] found significantly shorter median sleep onset latency

with homeopathic complex, with a significant change from baseline in the homeopathic complex group but not the placebo group. Hachul et al.[135] found a smaller proportion of women reported moderate or intense insomnia with isoflavone than with placebo ($p<0.01$).

Secondary Outcomes

Lin et al.[133] found no significant difference between Wuling capsule and placebo groups in physical, psychological, social, or environmental domains of the World Health Organization Quality of Life Brief Scale.

Passive stretching and yoga significantly improved (lowered) the Beck Depression Inventory and the Beck Anxiety Inventory compared with no treatment. Therapeutic massage significantly improved the Beck Depression Inventory and the Beck Anxiety Inventory at 8 weeks and 16 weeks compared with control treatment.

Adverse Effects

Evidence was insufficient to draw conclusions about the adverse effects of either of the approaches to treating insomnia. No significant differences were seen in overall withdrawals, withdrawals due to adverse effects, or the proportion of participants with at least one adverse effect between Wuling capsule and placebo groups. One participant withdrew from the Wuling capsule group because of an adverse effect. The most common adverse effects were dry mouth, dizziness, constipation, stomach bloating, stomach pain, and diarrhea.

Overall withdrawal did not differ significantly between homeopathic complex and placebo.

Hachul et al.[135] did not report withdrawals by treatment group, withdrawals due to adverse effects, or the proportion of participants with at least one adverse effect.

Significantly more overall withdrawals occurred in the passive stretching group than the control group. However, no withdrawals occurred due to adverse effects nor were there any adverse effects among participants receiving passive stretching or control treatment.

Oliveira et al.[139] did not report withdrawals by treatment group, withdrawals due to adverse effects, or adverse effects.

Comparative Effectiveness of Interventions of Different Types

Key Points

- A previous fair quality systematic review concluded that CBT-I is effective for treating insomnia when compared with drug treatments and the effects may be more durable than drugs.

Overview of Included Studies

We identified one relevant systematic review[141] (Table 29) and seven RCTs[125,142-146] that assessed the comparative effectiveness of different types of interventions. Mitchell et al. conducted a systematic literature review covering literature published through September of 2011.[141] They identified five RCTs with sufficient quality that compared drug treatments to CBT-I. Risk of bias of individual studies was conducted and the body of evidence was assessed with GRADE. We assessed the systematic review as fair quality. We did not identify RCTs

comparing drug treatments to CBT-I published after the search date of this review. We reiterate their conclusions and strength of evidence below in lieu of de novo extraction.

Table 29. Comparative effectiveness of CBT-I versus drugs: description and conclusions from previous systematic review

Study Information	Relevant Comparison	Author Conclusion [SR Evidence Quality] Strength of Evidence
Mitchell, 2012[141] 5 trials Literature search through October 2012 [Good]	CBT-I vs. benzodiazepines – short term treatment (3 RCTs)	CBT-I led to greater improvements. [Very Low] Insufficient
	CBT-I vs. benzodiazepines –long term treatment (3 RCTs)	CBT-I led to greater improvements. [Moderate] Moderate
	CBT-I vs. nonbenzodiazepines – short term treatment (2 RCTs)	CBT-I led to greater improvements. [Moderate] Moderate
	CBT-I vs. nonbenzodiazepines –long term treatment (1 RCT)	CBT-I led to greater improvements. [Low] Low

Evidence for each of these comparisons is insufficient to draw conclusions regarding comparative effectiveness. Two of the seven comparative effectiveness studies we identified addressed CBT-I to a pharmaceutical interventions and were not included in Mitchell et al.[28,144] The Morin et al. study was not included in Mitchell because it was an analysis of data collected in a previously included study.[28] The Morin et al. study. was not included in Mitchell et al. because the study did not assess the effectiveness of CBT-I.[144] This study compared CBT-I with CBT-I combined with zolpidem and found response rates similar in both groups. Rosen et al. randomized 40 participants to three treatments (estazolam and muscle relaxation; estazolam and guided imagery; and estalozam and sleep education) and found similar improvements across groups.[145]

Three trials compared a complementary and alternative treatment to a drug treatment. Huang et al.[142] randomized 180 participants to needle-rolling or clonazepam. They reported group difference in the PSQI post-treatment. Morin et al. compared a valerian-hops combination to diphenhydramine in 184 participants. Sleep parameters were no different between groups at 4 weeks, but quality of life was better with valerian-hops. Tu et al. randomized 33 participants to acupuncture or zolpidem. Evidence from these trials is insufficient to draw conclusions regarding comparative effectiveness.

Discussion

We systematically searched and synthesized the literature on a comprehensive set of interventions for insomnia disorder. Most trials assessed efficacy in the general adult population. We found low to moderate-strength evidence for the efficacy of certain psychological and pharmacologic interventions for some outcomes. Evidence on a variety of CAM interventions was insufficient to assess the efficacy of these interventions.

The strongest evidence for efficacy in the general adult population is for CBT-I across a variety of delivery modes. CBT-I improved global outcomes by minimum important differences when clearly established and otherwise by statistical measures. It also improved all sleep outcomes. Evidence was insufficient to compare CBT-I delivery modes. However, the range of modes available should enhance access to CBT-I. Evidence was not as robust for other psychological interventions because there were far fewer studies that assessed the same treatment and passive control in similar populations, and sample sizes were typically small. Psychological interventions are noninvasive and assumed to be low-harm interventions, but the studies were not good about recording withdrawals and often reported withdrawals in the overall population as opposed to withdrawals by group. Withdrawals are more likely due to intervention feasibility (i.e., requires too much time) than to physical or psychological harms, but reporting this information would improve understanding the feasibility of these interventions in practice.

We also found low to moderate-strength evidence of efficacy of nonbenzodiazepine hypnotics in the general adult population. These are the most commonly used medications for insomnia. Eszopiclone (Lunesta), zolpidem (Ambien), and zaleplon (Sonata) improved sleep outcomes. Few pharmaceutical trials measured and reported global outcomes; however, low-strength evidence suggests that eszopiclone, 2 and 3 mg, zolpidem ‘as needed’improve global outcomes. Eszopiclone and zolpidem achieved larger improvements in sleep outcomes than zaleplon, Results for adverse effects were mixed and often not different from placebo. However, most RCTs had duration shorter than drug therapy is used in practice. It is possible that these RCTs did not capture rare serious adverse effects associated with long-term use.

Evidence for other drug classes was limited. Melatonin PR showed a small improvement in one sleep outcome, but the improvement in sleep onset latency was modest (average decrease of 6 minutes). Low-strength evidence shows that ramelteon did not improve sleep outcomes when compared with placebo. Few efficacy studies of benzodiazepine hypnotics and antidepressants met inclusion criteria. We had few findings for these drugs.

The efficacy of insomnia interventions in older adults is assessed separately because their symptoms tend to differ from those of younger adults. Specifically, compared to younger adults, older adults are more likely to report waking after sleep onset more that sleep onset latency. In addition, older adults are often more sensitive to medications and their side effects, which can more easily become serious. Psychological interventions (CBT-I, BBT, and other multicomponent behavioral interventions) improve global outcomes (but not by minimum important differences) and sleep outcomes in older adults. Evidence is insufficient to assess adverse effects. A very limited number of pharmacologic studies enrolled only older adults. From these, we found low-strength evidence that low doses of eszopiclone and zolpidem improved some sleep outcomes in older adults without significantly different adverse effects from placebo.

Applicability

Participants enrolled in the trials included in this review appear to accurately reflect the population with insomnia disorder in terms of age and gender of included participants. However, participants in the psychological intervention trials may better reflect the insomnia disorder population because this population is likely to have other diseases and conditions and be on medications. The pharmacologic intervention trials were more likely to exclude these types of patients. Applicability of these results also depends on the accuracy of the diagnosis. We included studies where participants had a clinical diagnosis of insomnia; most studies used the DSM criteria. It is not clear that primary care or general mental health providers use these criteria to diagnose insomnia disorder and may turn to use drugs when patients complain of sleep problems without first ruling out other medical conditions or sleep disorders that might contribute to sleep problems.

Limitations

Current evidence has several limitations. First, data were limited for specific comparisons, despite having a large number of eligible studies. RCTs of psychological interventions contained a wide variety of intervention and control conditions limiting the data available to analyze similar comparisons. Older psychological studies were often underpowered and did not provide data sufficient for analysis (no group sample sizes, outcomes presented graphically without confidence intervals, etc.). Few trials measured and reported global outcomes. Insomnia disorder requires select sleep symptoms accompanied by daytime dysfunction or distress. Most trials measured only sleep outcomes which may not accurately reflect overall impact. This lack is especially important given the daytime symptoms that often accompany hypnotic drugs. Recent trials are more likely to report global outcomes. Also, we found little evidence establishing and using minimum important differences in this population. Although remission and response have been established for some instruments, they have not been consistently used. Sleep parameters are commonly reported in insomnia efficacy and comparative effectiveness trials. However, the literature contains few established minimum important differences for use in assessing efficacy and effectiveness. It was not clear how many minutes reduction in sleep onset latency, total sleep time, or wake time after sleep onset indicated clinical improvement. Sleep efficiency and sleep quality provided comprehensive measures of sleep and established minimum important differences or standardized effect size guidance eased interpretation of these measures.

Eligible drug trials rarely lasted longer than 6 weeks. Individuals taking medications for sleep often stay on the medications for months to years. Our review was designed to detect short term adverse effects associated with these drugs. Findings of safety in our review do not rule out the risk of serious adverse events associated with long-term use or rare adverse events. To gain an accurate synthesis of these adverse events would need to collect data from grey literature and observational studies. However, such studies have significant risk of selection bias and confounding. Previous research has summarized these adverse effects. Using pooled analyses of RCT data submitted to the FDA, Kripke et al. found increased incidence of depression[147] and skin cancer[148] among participants using nonbenzodiazepine hypnotics and ramelteon compared with placebo. Carson et al.[30] conducted a systematic review that included observational studies and case reports of nonbenzodiazepine hypnotics. In observational studies lasting 6-months to 1 year, Carson et al. found eszopiclone and zaleplon were associated with mild to moderate

adverse effects, while zolpidem was associated with serious adverse effects such as amnesia, vertigo, confusion, and diplopia.[30]

Future Research Needs

Future research to improve our understanding of treatments for insomnia disorder should include:

- Conceptual research to establish minimum important differences in sleep outcomes.
- Increased use of global outcomes of insomnia treatment.
- Use of global outcomes definitions that incorporate minimum important differences (remitters and responders).
- Head-to-head comparisons of drugs.
- Drug trials with treatment durations of one year or more, durations adequate to assess efficacy and comparative effectiveness of a chronic condition.
- Systematic review of observational studies to evaluate harms associated with long-term use of medications for insomnia disorder.

Table 30. Future research needs

Key Question	Results of Literature Review	Types of Studies; Needed to Answer Question	Future Research Recommendations
KQ1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?	Moderate strength evidence shows that global outcomes improve with CBT-I and certain medications. Little information was available to assess combination treatments and head to head comparisons.	RCTs	RCTs should be conducted that capture global outcomes and compare combination treatments and head to head comparisons.
a. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in older adults?	A very limited number of trials had long term outcomes; more research is needed.	RCTs	Additional long-term trials on the efficacy of evidence-based treatments to investigate factors associated with sustained improvements from psychological interventions.
b. What are the efficacy and comparative effectiveness of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for the treatment of insomnia disorder in adults?	Few trials were identified to analyze combination treatments (across intervention classes).	RCTs	RCTs that assess the efficacy and comparative effectiveness of short-term drug therapy combined with long-term CBT-I.
c. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in adults?	Few trials were identified. One systematic review concluded that CBT-I was superior to drug treatment for insomnia disorder.	RCTs	RCTs that compare various delivery modes of CBT-I to drug treatments.
KQ2. What are the harms of treatments for insomnia disorder in adults?	Harms were not always reported, especially in psychological and CAM trials.	Cohort studies	Cohort studies that reflect actual drug usage and systematically collect data on all harms.
a. What are the harms of treatments for insomnia disorder in older adults?	Evidence on long term harms were limited.	Systematic review of observational studies and open label RCTs.	A comprehensive assessment of medication harms that reflects actual use.
b. What are the harms of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for insomnia disorder in adults?	Limited data.	RCTs	RCTs that systematically collect harms data.
c. What are the long-term harms of treatments for insomnia disorder in adults?	Very limited data.	Systematic review of observational studies and open label RCTs.	A comprehensive assessment of medication harms that reflects actual use.

Conclusions

Our review found a large number of trials and low to moderate strength evidence supporting several interventions for insomnia disorder. Our results are consistent with other reviews concluding the efficacy of CBT-I and BBT for insomnia disorder and strengthens results from previous reviews concluding the efficacy of nonbenzodiazepines for insomnia disorder. The lack of available data on the long-term harms of these medication is a concern that needs to be addressed with future research. Similarly, studies of psychological treatments should better capture and report study withdrawals. These interventions have a low risk for harms, but they do require time and engagement from patients. This information would enhance understanding of the feasibility of these interventions in the general population.

Overall, several options exist to treat insomnia disorder in adults and older adults. Psychological approaches may be more sustainable and are less likely to lead to harms. Treatment offers global improvement as well as improved sleep to insomnia sufferers.

References

1. Morin CM, Benca R. Chronic insomnia. Lancet 2012; Mar;379(9821):1129-41. PMID: WOS:000302131800035.
2. Guideline Development Group for the management of patients in primary care. Clinical Practice Guidelines for the Management of Patients with Insomnia in Primary Care; National Health System Quality Plan, Ministry of Health and Social Policy. Health Technology Assessment Unit; Lain Entralgo Agency; . Community of Madrid. 2009.
3. American Psychiatric Association. Sleep-Wake Disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
4. Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep Med Rev 2010; Feb;14(1):69-82. PMID: 19962922.
5. Kraus SS, Rabin LA. Sleep America: Managing the crisis of adult chronic insomnia and associated conditions. J Affect Disord 2012; May;138(3):192-212. PMID: WOS:000302663900002.
6. Buysse DJ. Insomnia. Jama 2013; Feb 20;309(7):706-16. PMID: 23423416.
7. DynaMed [Internet]. Insomnia. EBSCO Information Services. 1995 – Accessed December 5, Registration and login required.
8. Montgomery P, Dennis Jane A. Cognitive behavioural interventions for sleep problems in adults aged 60+. John Wiley & Sons, Ltd. 2003. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003161/abstract. Accessed 1.
9. Xu M, Belanger L, Ivers H, et al. Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. Sleep Med 2011; 12(1):65-9. PMID: 21147026.
10. Rybarczyk B, Lund HG, Garroway AM, et al. Cognitive Behavioral Therapy for Insomnia in Older Adults: Background, Evidence, and Overview of Treatment Protocol. Clinical Gerontologist 2013; Jan;36(1):70-93. PMID: WOS:000312700500005.
11. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 2010; Nov;24(11):1577-601. PMID: 20813762.
12. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; Oct 15;4(5):487-504. PMID: 18853708.
13. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. Sleep 2006; Nov;29(11):1415-9. PMID: 17162987.
14. AASM. Personal Communication; 2013.
15. Baillargeon L, Landreville P, Verreault R, et al. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. Canadian Medical Association Journal 2003; Nov;169(10):1015-20. PMID: WOS:000186592000008.
16. Espie CA. "Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. Sleep 2009; 32(12):1549-58. PMID: 20041590.
17. Zhao K. Acupuncture for the treatment of insomnia. Int Rev Neurobiol 2013; 111:217-34. PMID: 24215925.
18. Xie CL, Gu Y, Wang WW, et al. Efficacy and safety of Suanzaoren decoction for primary insomnia: a systematic review of randomized controlled trials. BMC Altern Med 2013; 13:18. PMID: 23336848.
19. Yeung W-F, Chung K-F, Poon MM-K, et al. Prescription of Chinese herbal medicine and selection of acupoints in pattern-based traditional Chinese medicine treatment for insomnia: a systematic review. Evidence-Based Complementary and Alternative Medicine 2012; 2012.
20. Yeung WF, Chung KF, Poon MM, et al. Chinese herbal medicine for insomnia: a systematic review of randomized controlled trials. Sleep Med Rev 2012; Dec;16(6):497-507. PMID: 22440393.
21. Yeung WF, Chung KF, Poon MM, et al. Acupressure, reflexology, and auricular acupressure for insomnia: a systematic review of randomized controlled trials. Sleep Med 2012; Sep;13(8):971-84. PMID: 22841034.
22. Fismer KL, Pilkington K. Lavender and sleep: A systematic review of the evidence. European Journal of Integrative Medicine 2012; Dec;4(4):E436-E47. WOS:000312093100011.
23. Cheuk DK, Yeung WF, Chung KF, et al. Acupuncture for insomnia. Cochrane Database Syst Rev 2012; 9:CD005472. PMID: 22972087.
24. Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. Sleep Med Rev 2011; Apr;15(2):99-106. PMID: 20965131.

25. Lee J, Han M, Chung Y, et al. Effects of foot reflexology on fatigue, sleep and pain: a systematic review and meta-analysis. Journal Korean acad 2011; Dec;41(6):821-33. PMID: 22310867.
26. Ernst E, Lee MS, Choi TY. Acupuncture for insomnia? An overview of systematic reviews. Eur J Gen Pract 2011; Jun;17(2):116-23. PMID: 21463162.
27. Kleinman L, Buysse DJ, Harding G, et al. Patient-reported outcomes in insomnia: development of a conceptual framework and endpoint model. Behav Sleep Med 2013; 11(1):23-36. PMID: 23347114.
28. Morin CM. Measuring outcomes in randomized clinical trials of insomnia treatments. Sleep Med Rev 2003; Jun;7(3):263-79. PMID: 12927124.
29. Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and Management of Chronic Insomnia in Adults. Summary, Evidence Report/Technology Assessment no. 125. (Prepared by the Alberta Evidence-based Practice Center, under Contract No. C400000021.) AHRQ Publication No. 05-E021-1. Rockville, MD. 2005.
30. Carson S, McDonagh M, Thakurta S. Drug Class Review: Newer Drugs for Insomnia: Final Report Update 2 [Internet]. Portland (OR): Oregon Health & Science University (www. ncbi. nlm. nih. gov/books/NBK47207) 2008.
31. Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. Canadian Medical Association Journal 2000; 162(2):225-33.
32. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep 2006; Nov;29(11):1398-414. PMID: 17162986.
33. Morin CM, Hauri PJ, Espie CA, et al. Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. Sleep 1999; Dec 15;22(8):1134-56. PMID: 10617176.
34. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.2. 2012.
35. White C, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. 2009. http://effectivehealthcare.ahrq.gov/repFiles/methodsguide/systematicreviewsreplacedenovo.pdf.
36. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions: AHRQ. 2012.
37. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0: The Cochrane Collaboration; 2011.
38. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology 2011; Nov;64(11):1187-97. PMID: 21477993.
39. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res (Hoboken) 2011; Nov;63 Suppl 11:S287-96. PMID: 22588751.
40. Morin CM, Beaulieu-Bonneau S, LeBlanc M, et al. Self-help treatment for insomnia: a randomized controlled trial. Sleep 2005; Oct;28(10):1319-27. PMID: 16295218.
41. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep 2004; Dec 15;27(8):1567-96. PMID: 15683149.
42. Bastien CH, Fortier-Brochu E, Rioux I, et al. Cognitive performance and sleep quality in the elderly suffering from chronic insomnia. Relationship between objective and subjective measures.[Erratum appears in J Psychosom Res. 2003 Nov;55(5):475]. J Psychosom Res 2003; Jan;54(1):39-49. PMID: 12505554.
43. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. 2013.
44. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010 December. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412. Accessed AHRQ Publication No. 11-EHC019-EF.
45. Arnedt JT, Cuddihy L, Swanson LM, et al. Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia. Sleep 2013; Mar;36(3):353-62. PMID: 23450712.
46. Bjorvatn B, Fiske E, Pallesen S. A self-help book is better than sleep hygiene advice for insomnia: a randomized controlled comparative study. Scand J Psychol 2011; Dec;52(6):580-5. PMID: 21790620.

47. Edinger J, Sampson W. A primary care "friendly" cognitive behavioral insomnia therapy. Sleep 2003; 26(2):177-82.
48. Edinger JD, Olsen MK, Stechuchak KM, et al. Cognitive behavioral therapy for patients with primary insomnia or insomnia associated predominantly with mixed psychiatric disorders: a randomized clinical trial. Sleep 2009; Apr;32(4):499-510. PMID: 19413144.
49. Espie CA, Inglis SJ, Tessier S, et al. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. Behaviour Research and Therapy 2001. Jan;39(1):45-60. PMID: WOS:000165850000004.
50. Espie CA, Kyle SD, Williams C, et al. A Randomized, Placebo-Controlled Trial of Online Cognitive Behavioral Therapy for Chronic Insomnia Disorder Delivered via an Automated Media-Rich Web Application. Sleep 2012; Jun;35(6):769-81. WOS:000304767300015.
51. Espie CA, MacMahon KM, Kelly H-L, et al. Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice. Sleep: Journal of Sleep and Sleep Disorders Research 2007; May;30(5):574-84.
52. Jansson M, Linton SJ. Cognitive-behavioral group therapy as an early intervention for insomnia: a randomized controlled trial. Journal of Occupational Rehabilitation 2005; Jun;15(2):177-90. PMID: 15844675.
53. Jansson-Frojmark M, Linton SJ, Flink IK, et al. Cognitive-behavioral therapy for insomnia co-morbid with hearing impairment: a randomized controlled trial. J Clin Psychol Med Settings 2012; Jun;19(2):224-34. PMID: 22323041.
54. Mimeault V, Morin CM. Self-help treatment for insomnia: bibliotherapy with and without professional guidance. J Consult Clin Psychol 1999; Aug;67(4):511-9. PMID: 10450621.
55. Morgan K, Dixon S, Mathers N, et al. Psychological treatment for insomnia in the management of long-term hypnotic drug use: a pragmatic randomised controlled trial. Br J Gen Pract 2003; Dec;53(497):923-8. PMID: 14960215.
56. Pigeon WR, Moynihan J, Matteson-Rusby S, et al. Comparative effectiveness of CBT interventions for co-morbid chronic pain & insomnia: a pilot study. Behav Res Ther 2012; Nov;50(11):685-9. PMID: 22982083.
57. Ritterband LM, Thorndike FP, Gonder-Frederick LA, et al. Efficacy of an Internet-based behavioral intervention for adults with insomnia.[Erratum appears in Arch Gen Psychiatry. 2010 Mar;67(3):311]. Archives of General Psychiatry 2009; Jul;66(7):692-8. PMID: 19581560.
58. Strom L, Pettersson R, Andersson G. Internet-based treatment for insomnia: a controlled evaluation. J Consult Clin Psychol 2004; Feb;72(1):113-20. PMID: 14756620.
59. van Straten A, Cuijpers P, Smit F, et al. Self-help treatment for insomnia through television and book: a randomized trial. Patient Educ Couns 2009; Jan;74(1):29-34. PMID: 18801639.
60. Vincent N, Lewycky S. Logging on for better sleep: RCT of the effectiveness of online treatment for insomnia. Sleep 2009; Jun;32(6):807-15. PMID: 19544758.
61. Morgan K, Gregory P, Tomeny M, et al. Self-help treatment for insomnia symptoms associated with chronic conditions in older adults: a randomized controlled trial. J Am Geriatr Soc 2012; Oct;60(10):1803-10. PMID: 23035962.
62. Morin C, Colecchi C, Stone J, et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. J Am Med Assoc 1999; 281(11):991-9. PMID.
63. Morin CM, Kowatch RA, Barry T, et al. Cognitive-behavior therapy for late-life insomnia. J Consult Clin Psychol 1993; Feb;61(1):137-46. PMID: 8450099.
64. Rybarczyk B, Lopez M, Benson R, et al. Efficacy of two behavioral treatment programs for comorbid geriatric insomnia. Psychol Aging 2002; Jun;17(2):288-98. PMID: 12061413.
65. Vitiello MV, McCurry SM, Shortreed SM, et al. Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the lifestyles randomized controlled trial. J Am Geriatr Soc 2013; Jun;61(6):947-56. PMID: 23711168.
66. Vitiello MV, Rybarczyk B, Von Korff M, et al. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. J Clin Sleep Med 2009; Aug 15;5(4):355-62. PMID: 19968014.
67. Morin CM, Mimeault V, Gagne A. Nonpharmacological treatment of late-life insomnia. J Psychosom Res 1999; Feb;46(2):103-16. PMID: 10098820.

68. Morawetz D. Behavioral self-help treatment for insomnia - a controlled evaluation. Behav 1989; Sum;20(3):365-79. WOS:A1989AJ72500006.
69. Woolfolk RL, McNulty TF. Relaxation treatment for insomnia - a component analysis. Journal of Consulting and Clinical Psychology 1983; 1983;51(4):495-503. WOS:A1983RA97900004.
70. Buysse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch Intern Med 2011; May 23;171(10):887-95. PMID: 2011292008.
71. Germain A, Moul DE, Franzen PL, et al. Effects of a brief behavioral treatment for late-life insomnia: Preliminary findings. J Clin Sleep Med 2006; 15 Oct;2(4):403-6. PMID: 2006565250.
72. McCrae CS, McGovern R, Lukefahr R, et al. Research Evaluating Brief Behavioral Sleep Treatments for Rural Elderly (RESTORE): a preliminary examination of effectiveness. Am J Geriatr Psychiatry 2007; Nov;15(11):979-82. PMID: 17974868.
73. Soeffing JP, Lichstein KL, Nau SD, et al. Psychological treatment of insomnia in hypnotic-dependant older adults. Sleep Med 2008; Jan;9(2):165-71. PMID: 17644419.
74. Epstein DR, Sidani S, Bootzin RR, et al. Dismantling multicomponent behavioral treatment for insomnia in older adults: a randomized controlled trial. Sleep 2012; Jun;35(6):797-805. PMID: 22654199.
75. Friedman L, Benson K, Noda A, et al. An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. Journal of Geriatric Psychiatry and Neurology 2000; Spr;13(1):17-27. WOS:000085979100003.
76. Riedel BW, Lichstein KL, Dwyer WO. Sleep compression and sleep education for older insomniacs - self-help versus therapist guidance. Psychology and Aging 1995; Mar;10(1):54-63. WOS:A1995QN04500007.
77. Davies R, Lacks P, Storandt M, et al. Countercontrol treatment of sleep-maintenance insomnia in relation to age. Psychology and aging 1986; 1986-Sep;1(3):233-8. PMID: 3267403.
78. Espie C, Lindsay W, Brooks D, et al. A controlled comparative investigation of psychological treatments for chronic sleep-onset insomnia. Behav Res Ther 1989; 27(1):79-88.
79. Morin CM, Azrin NH. Stimulus-control and imagery training in treating sleep-maintenance insomnia. Journal of Consulting and Clinical Psychology 1987; Apr;55(2):260-2. WOS:A1987G665500021.
80. Riedel BW, Lichstein KL, Peterson BA, et al. A comparison of the efficacy of stimulus control for mediated and nonmedicated insomniacs. Behavior Modification 1998; Jan;22(1):3-28. WOS:000071373800001.
81. Schoicket SL, Bertelson AD, Lacks P. Is sleep hygiene a sufficient treatment for sleep-maintenance insomnia. Behav 1988; Spr;19(2):183-90. WOS:A1988N534400007.
82. Morin CM, Azrin NH. Behavioral and cognitive treatments of geriatric insomnia. Journal of Consulting and Clinical Psychology 1988; Oct;56(5):748-53. WOS:A1988Q401700016.
83. Puder R, Lacks P, Bertelson AD, et al. Short-term stimulus-control treatment of insomnia in older adults. Behav 1983; 1983;14(3):424-9. WOS:A1983QV49500007.
84. Lacks P, Bertelson A, Gans L, et al. The effectiveness of three behavioral treatments for different degrees of sleep onset insomnia. Behav Ther 1983; 14(5):593-605.
85. Bastien CH, Morin CM, Ouellet MC, et al. Cognitive-behavioral therapy for insomnia: comparison of individual therapy, group therapy, and telephone consultations. J Consult Clin Psychol 2004; Aug;72(4):653-9. PMID: 15301650.
86. Rybarczyk B, Mack L, Harris JH, et al. Testing two types of self-help CBT-I for insomnia in older adults with arthritis or coronary artery disease. Rehabil Psychol 2011; Nov;56(4):257-66. PMID: 22121936.
87. Edinger J, Wohlgemuth W, Radtke R, et al. Cognitive behavioral therapy for treatment of chronic primary insomnia: A randomized controlled trial. J Am Med Assoc 2001; 285(14):1856-64.
88. Lichstein KL, Riedel BW, Wilson NM, et al. Relaxation and sleep compression for late-life insomnia: A placebo-controlled trial. Journal of Consulting and Clinical Psychology 2001; 69(2):227-39.
89. Pech M, O'Kearney R. A randomized controlled trial of problem-solving therapy compared to cognitive therapy for the treatment of insomnia in adults. Sleep 2013; 01 May;36(5):739-49. PMID: 2013288325.
90. Rybarczyk B, Lopez M, Schelble K, et al. Home-based video CBT for comorbid geriatric insomnia: a pilot study using secondary data analyses. Behav Sleep Med 2005; 3(3):158-75. PMID: 15984917.
91. Jansson-Frojmark M, Lind M, Sunnhed R. Don't worry, be constructive: a randomized controlled feasibility study comparing behaviour therapy singly and combined with constructive worry for insomnia. Br J Clin Psychol 2012; Jun;51(2):142-57. PMID: 22574800.

92. Riley WT, Mihm P, Behar A, et al. A computer device to deliver behavioral interventions for insomnia. Behav Sleep Med 2010; 8(1):2-15. PMID: 20043245.
93. Lack L, Wright H, Paynter D. The treatment of sleep onset insomnia with bright morning light. Sleep and Biological Rhythms 2007; Jul;5(3):173-9.
94. Kirisoglu C, Guilleminault C. Twenty minutes versus forty-five minutes morning bright light treatment on sleep onset insomnia in elderly subjects. J Psychosom Res 2004; May;56(5):537-42. PMID: 15172210.
95. Friedman L, Zeitzer JM, Kushida C, et al. Scheduled bright light for treatment of insomnia in older adults. J Am Geriatr Soc 2009; Mar;57(3):441-52. PMID: 19187411.
96. Krystal A, Walsh J, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep 2003; 26(7):793-9.
97. Walsh JK, Krystal AD, Amato DA, et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. Sleep 2007; Aug;30(8):959-68. PMID: 17702264.
98. Zammit GK, McNabb LJ, Caron J, et al. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. Curr Med Res Opin 2004; Dec;20(12):1979-91. PMID: 15701215.
99. Elie R, Ruther E, Farr I, et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. J Clin Psychiatry 1999; 60(8):536-44.
100. Fry J, Scharf M, Mangano R, et al. Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. Int Clin Psychopharmacol 2000; 15(3):141-52.
101. Lahmeyer H, Wilcox C, Kann J, et al. Subjective efficacy of zolpidem in outpatients with chronic insomnia: double blind comparison with placebo. Clin Drug Invest 1997; 13:134-44.
102. Scharf M, Roth T, Vogel G, et al. A multicenter placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry 1994; 55(5):192-9.
103. Allain H, Arbus L, Schuck S. Efficacy and safety of zolpidem administered as needed in primary insomnia: results of a double-blind, placebo-controlled study. Clin Drug Invest 2001; 21(6):391-4000.
104. Perlis ML, McCall WV, Krystal AD, et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. J Clin Psychiatry 2004; Aug;65(8):1128-37. PMID: 15323600.
105. Walsh J. Zolpidem "as needed" for the treatment of primary insomnia: a double-blind, placebo-controlled study. Sleep Med Rev 2002; 6:S7-11.
106. Roth T, Krystal A, Steinberg FJ, et al. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. Sleep 2013; Feb;36(2):189-96. PMID: 23372266.
107. Krystal AD, Erman M, Zammit GK, et al. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sleep 2008; Jan;31(1):79-90. PMID: 18220081.
108. Ancoli-Israel S, Krystal AD, McCall WV, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. Sleep 2010; Feb;33(2):225-34. PMID: 20175406.
109. Leppik I, Roth-Schechter G, Gray G, et al. Double blind, placebo controlled comparison of zolpidem, triazolam, and temazepam in elderly patients with insomnia. Drug Dev Res 1997; 40:230-8.
110. Wade AG, Crawford G, Ford I, et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. Curr Med Res Opin 2011; Jan;27(1):87-98. PMID: 21091391.
111. Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. BMC Med 2010; 8:51. PMID: 20712869.
112. Kuriyama A, Honda M, Hayashino Y. Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. Sleep Med 2014; 15(4):385-92.
113. Mayer G, Wang-Weigand S, Roth-Schechter B, et al. Efficacy and Safety of 6-Month Nightly Ramelteon Administration in Adults with Chronic Primary Insomnia. Sleep 2009; Mar;32(3):351-60. WOS:000263705500009.

114. Uchimura N, Ogawa A, Hamamura M, et al. Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study. Expert rev 2011; Feb;11(2):215-24. PMID: 21306209.
115. Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia.[Erratum appears in J Clin Sleep Med. 2007 Oct 15;3(6):table of contents], [Erratum appears in J Clin Sleep Med. 2008 Oct 15;4(5):table of contents]. J Clin Sleep Med 2007; Aug 15;3(5):495-504. PMID: 17803013.
116. Roth T, Seiden D, Sainati S, et al. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 2006; Jun;7(4):312-8. WOS:000238523200003.
117. Mitler M, Seidel W, van den Hoed J, et al. Comparative hypnotic effects of flurazepam, triazolam, and placebo: a long-term simultaneous nighttime and daytime study. J Clin Psychopharmacol 1984; 4(1):2-13.
118. Minnekeer R, Marchal J, Van de Velde L, et al. A double-blind study comparing the efficacy and safety of quazepam with flunitrazepam and placebo in patients with chronic insomnia. Acta Ther 1988; 14(2):159-70.
119. Wu R, Bao J, Zhang C, et al. Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. Psychother Psychosom 2006; 75(4):220-8. PMID: 16785771.
120. Reeves R. Comparison of triazolam, flurazepam and placebo as hypnotics in geriatric patients with insomnia. J Clin Pharmacol 1977; 17:319-23.
121. Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treatment of primary insomnia - a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry 2001; 62(6):453-63.
122. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep 2011; Oct;34(10):1433-42. PMID: 21966075.
123. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia. Sleep 2010; Nov;33(11):1553-61. WOS:000285212600019.
124. Lankford A, Rogowski R, Essink B, et al. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med 2012; Feb;13(2):133-8. WOS:000301695500003.
125. Zavesicka L, Brunovsky M, Horacek J, et al. Trazodone improves the results of cognitive behaviour therapy of primary insomnia in non-depressed patients. Neuroendocrinol Lett 2008; Dec;29(6):895-901. PMID: 19112384.
126. Voshaar RCO, Van Balkom AJLM, Zitman FG. Zolpidem is not superior to temazepam with respect to rebound insomnia: A controlled study. Eur Neuropsychopharmacol 2004; August;14(4):301-6. PMID: 2004220776.
127. Hachul H, Garcia TKP, MacIel AL, et al. Acupuncture improves sleep in postmenopause in a randomized, double-blind, placebo-controlled study. Climacteric 2013; February;16(1):36-40. PMID: 2013045144.
128. Huo ZJ, Guo J, Li D. Effects of acupuncture with meridian acupoints and three Anmian acupoints on insomnia and related depression and anxiety state. Chin J Integr Med 2013; Mar;19(3):187-91. PMID: 22903446.
129. Zhang YF, Ren GF, Zhang XC. Acupuncture plus cupping for treating insomnia in college students. J Tradit Chin Med 2010; Sep;30(3):185-9. PMID: 21053624.
130. Cooper KL, Relton C. Homeopathy for insomnia: summary of additional RCT published since systematic review. Sleep Med Rev 2010; Dec;14(6):411. PMID: 20817511.
131. Taibi DM, Landis CA, Petry H, et al. A systematic review of valerian as a sleep aid: safe but not effective. Sleep Med Rev 2007; Jun;11(3):209-30. PMID: 17517355.
132. Cooper KL, Relton C. Homeopathy for insomnia: a systematic review of research evidence. Sleep Med Rev 2010; Oct;14(5):329-37. PMID: 20223686.
133. Lin Y, Wang XY, Ye R, et al. Efficacy and safety of Wuling capsule, a single herbal formula, in Chinese subjects with insomnia: a multicenter, randomized, double-blind, placebo-controlled trial. J Ethnopharmacol 2013; Jan 9;145(1):320-7. PMID: 23178661.
134. Zick SM, Wright BD, Sen A, et al. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study. BMC Altern Med 2011; 11:78. PMID: 21939549.
135. Hachul H, Brandao LC, D'Almeida V, et al. Isoflavones decrease insomnia in postmenopause. Menopause 2011; Feb;18(2):178-84. PMID: 20729765.
136. Afonso RF, Hachul H, Kozasa EH, et al. Yoga decreases insomnia in postmenopausal women: a randomized clinical trial. Menopause 2012; Feb;19(2):186-93. PMID: 22048261.

137. Abbasi B, Kimiagar M, Sadeghniiat K, et al. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. Journal of Research in Medical Sciences 2012; 17(12):1161-9. PMID: 2013170468.
138. Harrison CC, Solomon EM, Pellow J. The effect of a homeopathic complex on psychophysiological onset insomnia in males: a randomized pilot study. Altern Ther Health Med 2013; Sep-Oct;19(5):38-43. PMID: 23981403.
139. Oliveira DS, Hachul H, Goto V, et al. Effect of therapeutic massage on insomnia and climacteric symptoms in postmenopausal women. Climacteric 2012; Feb;15(1):21-9. PMID: 22017318.
140. Lin W-C. Cognitive behavioral treatment for insomnia on cancer patients: A systematic review. Chinese Journal of Psychology 2010; Jun;52(2):173-88. PMID: 2012-09517-004.
141. Mitchell MD, Gehrman P, Perlis M, et al. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract 2012; 13:40. PMID: 22631616.
142. Huang LS, Wang DL, Wang CW, et al. The needle-rolling therapy for treatment of non-organic chronic insomnia in 90 cases. J Tradit Chin Med 2009; Mar;29(1):19-23. PMID: 19514183.
143. Morin CM, Koetter U, Bastien C, et al. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep 2005; Nov;28(11):1465-71. PMID: 16335333.
144. Morin CM, Vallieres A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. Jama 2009; May 20;301(19):2005-15. PMID: 19454639.
145. Rosen RC, Lewin DS, Goldberg L, et al. Psychophysiological insomnia: combined effects of pharmacotherapy and relaxation-based treatments. Sleep Med 2000; Oct 1;1(4):279-88. WOS:000208300700005.
146. Tu JH, Chung WC, Yang CY, et al. A comparison between acupuncture versus zolpidem in the treatment of primary insomnia. Asian J Psychiatr 2012; Sep;5(3):231-5. PMID: 22981051.
147. Kripke DF. Greater incidence of depression with hypnotic use than with placebo. BMC Psychiatry 2007; Aug;7. PMID: WOS:000250031000001.
148. Kripke DF. Possibility that certain hypnotics might cause cancer in skin. J Sleep Res 2008; Sep;17(3):245-50. PMID: 18844818.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BBT	Brief behavioral therapy
BDI	Beck Depression Inventory
CAM	Complementary and alternative medicine
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impression
CI	Confidence interval
DSM	Diagnostic and Statistical Manual
ESS	Epworth sleepiness scale
FSS	Fatigue Severity Scale
ICSD	International Classification of Sleep Disorders
ICTRP	International Controlled Trials Registry Platform
ISI	Insomnia Severity Index
MID	Minimum important difference
MOS	Medical Outcomes Sleep questionnaire
PGI	Patient Global Impression
PICOTS	Population, intervention, comparators, outcomes, timing, settings
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled trial
RD	Risk difference
RR	Risk ratio
SF-36	Short-form Health Survey
SIP	Scientific Information Packet
SMD	Standard mean difference
SOE	Strength of evidence
STAI	State-Trait Anxiety Inventory
WHOQOL	World Health Organization Quality of Life
WMD	Weighted mean difference